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# THE MEDICAL CLINICS OF NORTH AMERICA

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## SYMPOSIUM ON THE ADENOPATHIES

I W Held and A. Allen Goldbloom LYMPHADENOPATHY A CLINICAL INTERPRETATION

Lloyd F Craver THE TREATMENT OF THE MORE IMPORTANT LYMPHADENOPATHIES WITH SPECIAL REFERENCE TO IRRADIATION

CLINIC OF DRS I W HELD AND  
A ALLEN GOLDBLOOM

BETH ISRAEL HOSPITAL

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### LYMPHADENOPATHY, A CLINICAL INTERPRETATION

DESPITE the fact that adenopathy is frequently encountered and presents so leading a symptom as enlargement of the glands, its diagnosis is often most difficult. One of the reasons for this is that diseases of the lymph glands, until now, have not been approached from the point of view of functional disturbances caused by the underlying pathology in the gland, a method successfully employed in diseases of almost all other organs of the body. In adenopathy only disturbed hematopoietic function has been appreciated at the bedside. When there is hematological evidence of disease of the glands, the diagnosis, of course, is simple. But in many instances the hematological findings do not identify the disease and if the pathologic study of biopsy material is likewise without avail, the diagnosis remains undetermined.

It may seem, at first glance, that any attempt to determine the structural changes in the lymph gland from the evidences

of disturbed function would be futile, partly because pathologic changes are so often out of proportion to disturbed function, and *vice versa*, and partly because the degree of pathologic function varies with the stage of the disease. However, the clue is furnished in the fact that every organ in the body is made up of structural components that vary in the importance of their physiologic function. Pathologic function is most pronounced when the structural components with the most important physiologic function are diseased, and least so, when parts of minor functional importance are affected.

By keeping in mind the anatomy and functions of the various parts of the lymph gland, and by noting, in case of disease, which of these functions is disturbed, we believe much of the present diagnostic difficulty pertaining to the adenopathies will be eliminated.

#### ANATOMY AND PHYSIOLOGY OF THE LYMPHATIC SYSTEM

**Lymph Vessels, Nodules, and Nodes**—By the seventh month of intra-uterine life, small collections of elongated areas of lymphocytes have formed in the body. These structures contain, in addition to lymphocytes, isolated areas of reticulum. Many of the structures are interrupted in their course by small nodules, also containing lymphocytes and reticulum.

Early in postuterine life, these elongated areas become lymph vessels and capillaries. In addition to lymphocytes and reticulum, they now contain an endothelium derived, according to Sabin,<sup>1</sup> from the venules. Along the course of these vessels are lymph nodules, nodes and glands, which, during childhood and puberty, tend to disappear or atrophy.

**Lymph Glands**—The lymph glands constitute depots for the unloading of substances in the lymph that are unfit for the circulation. Of the two important fluids in the body, namely, blood and lymph, the former starts its circulation from the great motor, the heart, and runs through a closed system of vessels until it reaches the capillaries and then the tissues. Lymph, on the other hand, according to MacCallum<sup>2</sup>

and others, starts from the lymph spaces and is filtered through a layer of endothelium to reach the lymph capillaries. Lymph that is fit to enter the blood from the lymph capillaries does so by contiguity with adjacent venules. The remainder of the lymph passes through a closed system of vessels equipped with valves in order to prevent backflow, and through glands scattered along the course of the vessels until it reaches the thoracic duct on the right side, and the subclavian duct on

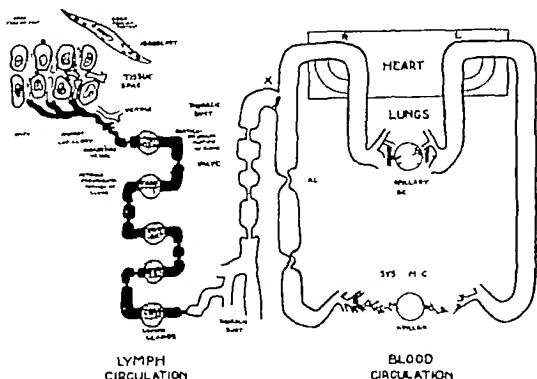


Diagram 1—Contrasting the lymph and the blood circulation. Note that the lymph loaded with effete cloudy material is filtered through numerous nodules and glands and its flow impeded by many valves before it is made innocuous enough to be emptied into the blood stream at point x.

the left, whence it enters the circulation. This detour serves the purpose of bringing the lymph to the blood in a purified state, all unsuitable substances having been deposited in nodes and lymph glands en route (Diagram 1). For diagnostic purposes, a knowledge of the distribution of the lymph glands throughout the body is essential (Table 1).

The lymph gland proper consists of three main parts: the capsule which serves as a filter for

TABLE 1

## REGIONAL DISTRIBUTION OF THE LYMPH GLANDS

<i>Head</i>	
Skin of the forehead	Antero-auricular glands
Parietal part of the skull	Postero auricular and occipital glands
Eyes	Inferior maxillary, buccal and antero-auricular glands
Ears	Postero auricular, posteropharyngeal, and deep cervical glands
Nose	Inferior maxillary, deep cervical and retro pharyngeal glands
<i>Arms</i>	
Skin	Axillary glands
Mammary glands	
(a) Lateral portion	Axillary, infraclavicular, and sternal glands
(b) Median portion	Sternal glands
Muscles	Axillary, sternal, and supraclavicular glands
<i>Esophagus</i>	Deep cervical, paratracheal, bronchial, postero mediastinal, and upper gastric glands
<i>Thorax and Pleura</i>	Intercostal and sternal glands
<i>Lungs</i>	Bronchopulmonary, tracheal, bronchial and glands at bifurcation of the aorta
<i>Heart and Thymus</i>	Anteromediastinal glands
<i>Diaphragm</i>	Anterosternal and posterosternal, mediastinal, and glands at bifurcation of the aorta
<i>Umbilicus</i>	Inferior epigastric and iliac glands
(a) Skin below umbilicus	Superficial inguinal glands
<i>Liver</i>	Hepatic, superficial gastric, aortic, splenic, pancreatic, anterosternal and anteromediastinal glands
<i>Gallbladder</i>	Pancreatic glands
<i>Pancreas</i>	Pancreatic, splenic, hepatic, superficial gastric, mesenteric and aortic glands
<i>Spleen</i>	Splenic and hepatic glands
<i>Duodenum</i>	Pancreatic and pancreaticoduodenal, jejunal, iliac, cecal, appendiceal and mesenteric glands
<i>Colon</i>	Mesocolic, gastric, splenic, and abdominal aortic glands
<i>Ureters</i>	Abdominal aortic, common iliac, hypogastric, and splenic glands
<i>Tubes and Ovaries</i>	Aortic and superficial inguinal glands
<i>Uterus</i>	Iliac and aortic glands
<i>Cervix</i>	Iliac glands
<i>Vagina</i> (a) Upper part	Hypogastric, iliac, and anorectal glands
(b) Lower part	Superficial inguinal and hypogastric glands
<i>Prostate</i>	External iliac, hypogastric, sacral, hemorrhoidal, and seminal vesicular glands, ductus deferens, hypogastric, testicular, epididymic and aortic glands

<i>Rectum</i> (a) External region	Superficial inguinal glands.
(b) Internal region	Anorectal and superficial hemorrhoidal glands
<i>Scrotum and labia</i>	Superficial inguinal glands.
<i>Penis</i>	Superficial deep inguinal and iliac glands.
<i>Lower Extremities</i>	
Hips	Deep inguinal hypogastric and external glands.
Deep parts	Superficial deep inguinal and popliteal glands
Skin	Superficial inguinal glands.

gland and has, also, a supportive function, the cortico-medullary portion and the reticulo-endothelium Anatomically

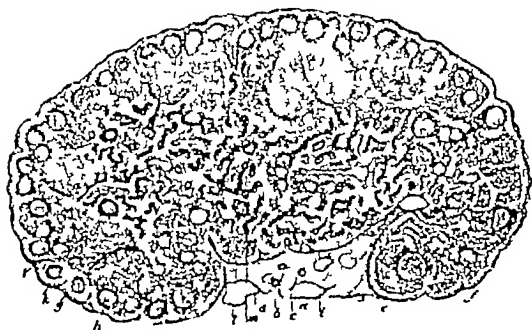


Fig 81—Microphotograph of a lymph gland *a* Hilus *b* arteriole *c* venous sinuses *d* adipose tissue *e* secondary nodule of cortex *f* vein in medulla *g* subcapsular lymph sinus *h* germinal center of secondary nodule *i* *j* trabeculae *k* capsule *l* lymph sinus *m* medullary cord (Radasch Manual of Histology, "P. Blakiston's Son and Co., Inc.")

the corticomedullary and reticulo-endothelial parts of the gland are interwoven, but, functionally, they are distinct.

The cortex of the gland is composed chiefly of secondary nodules separated from one another by trabeculae and sinuses. The secondary nodules in turn, consist of a germinal center, where mitosis occurs and a peripheral zone of closely packed lymphocytes. The medullary side of each nodule continues as a cordlike mass into the center of the gland where the

nodules anastomose to form medullary cords. Between the trabeculae and the medullary cords is a delicate reticulum, which marks the position of the sinuses continued from the cortex, the sinus being not a clear-cut space but a series of fine spaces between the trabeculae and the parenchyma of the organ (Fig 81). *The main function of the corticomedullary portion of the gland is to produce lymphocytes.*

The reticulo-endothelium consists of reticular fibers extending into the medullary portion and of endothelial cells lining the sinuses and subcapsular space. Anatomically, the reticulum and endothelium are quite different, but, as in the reticulo-endothelium elsewhere in the body, their functions are closely allied (Fig 81).

Throughout life, the reticulo-endothelium is the only part of the body to retain exactly certain of its embryonal functions, namely, connective tissue formation, histiocytosis, and hemapoiesis. According to Klemperer,<sup>3</sup> its phagocytic activity is evident in normal adult life and conspicuous in Gaucher's and Niemann-Pick's disease, it can be stimulated, also, by the experimental introduction of colloidal substances. Its hematopoietic activity, on the other hand, is not observable under normal conditions, but becomes apparent whenever an excessive demand has exhausted the supply of hematopoietic cells in the normal sites of blood formation.

The functional significance of the reticulo-endothelial system at large began to be most fully realized when Ribbert,<sup>4</sup> Goldmann,<sup>5</sup> and others developed vital and supravital cell staining methods, and when Aschoff,<sup>6</sup> and Landau and McNee<sup>7</sup> studied the intensity with which various stains are taken up by certain of the reticulo-endothelial cells (histiocytes) and their failure to be taken up by other cells (fibroblasts). It was found that, *in addition to hematopoietic function, one of the chief functions of the reticulo-endothelium is to store various electronegative colloids of an organic and inorganic nature, of exogenous and endogenous source, and of varying morphological consistency.* Among such substances are the

following Anode vital stains, metals, the colloid products of intermediary medullary metabolism, nonstaining colloid substances such as cholesterol and the lipoids, and coarse corpuscular elements such as pigments (coal, stone, etc.), bacteria, platelets, and clumps of bacterial elements

*In general, the function of the reticulo endothelial portion of the lymph gland is identical with that of the reticulo-endothelial system elsewhere in the body, but there are nevertheless, two outstanding differences. The first of these is that the absorptive and adsorptive processes in the lymph gland are much more rapid than in the reticulo endothelium at large. Secondly, although the integrity of the reticulo endothelial cells elsewhere is always restored following an invasion by foreign substances or bacteria (unless the invasion is overwhelming and the invader especially virulent), the reticulo endothelium of the lymph gland is permanently damaged by any such invasion. It is this permanent injury to the reticulo-endothelium of the gland, even by the slightest invasion of bacteria, that makes it so difficult for the pathologist to determine the primary cause of a lesion in the lymph gland unless the changes are specifically characteristic of tuberculosis, Hodgkin's disease, sarcoma, or carcinoma. Thus damage of the reticulo-endothelium is nature's sacrifice in an effort to safeguard the rest of the gland. In other words, the reticulo endothelium of the gland is her soldier of soldiers, just as the lymph glands at large constitute her first line of defense in case of disease.*

In the light of the foregoing, we are classifying adenopathies according to the portion of the gland in which the pathologic structural changes are most pronounced. *The two main divisions are Adenopathy primarily arising in the corticomedullary portion of the gland, and adenopathy originating chiefly in the reticulo-endothelium.* In addition, there may be adenopathy of the gland as a whole, secondary to infectious disease or secondary to primary hematopoietic disease, and adenopathy of an infiltrative type including adenopathies due to metabolic disturbances and carcinoma.



Whenever the corticomedullary portion is primarily affected, functional disturbance is evidenced by a change in the production of lymphocytes. This may be a qualitative or quantitative change, or both. The affection of this part of the gland may be secondary to disease elsewhere in the body, or it may be primary.

If the reticulo-endothelium is the seat of pathology, some or all of the functions originating in this part of the gland are disturbed, as, for example, hematopoiesis, absorption, adsorption, and immunity.

Should both the corticomedullary and reticulo-endothelial portions of the lymph gland be involved, mixed functional disturbance results. It is to be borne in mind throughout that pathology is not static but dynamic so that when a pathologic process invades a part of an organ, if the disease lasts long enough it inevitably spreads to another part of the organ and eventually affects the system functionally related to the organ. Therefore, pathology primarily affecting either the corticomedullary or the reticulo-endothelial portion can spread not only to the gland as a whole but may even involve the hematopoietic system, and does so in most of the chronic cases. This does not minimize, however, the value of classifying adenopathy according to structural changes with specific functional disturbances.

## CLASSIFICATION OF THE ADENOPATHIES

### *I Adenopathy Secondary to Local Infection*

### *II Adenopathy Secondary to Systemic Infection*

Scarlet fever

Rubella

Tularemia

Anthrax

Rheumatic fever

Anterior poliomyelitis

Typhoid

Primary mesenteric lymphadenitis

Tuberculosis

Lues

Chancroid

Lymphogranuloma inguinale

III *Adenopathy Confined Chiefly to the Corticomedullary Portion*

Pfeiffer's glandular fever  
Lymphatic leukemia  
Follicular lymphoblastoma  
Lymphosarcoma

IV *Adenopathy Confined Chiefly to the Reticulo-endothelium*

Infectious mononucleosis  
Monocytic leukemia  
Hodgkin's disease  
Leukosarcoma

V *Adenopathy of an Infiltrative Type*

Silicosis, anthracosis, and chalicosis  
Secondary to metabolic disturbances  
Gaucher's disease  
Niemann Pick's disease  
Xanthoma diabetorum  
Secondary to carcinoma

VI *Adenopathy Secondary to Primary Hematopoietic Disease*

Myelogenous leukemia

DIFFERENTIAL DIAGNOSIS BETWEEN ENLARGED LYMPH GLANDS  
AND OTHER TUMEFACTION

Before considering the diagnosis of the various adenopathies, it is essential first to determine that adenopathy exists.

Simple as the diagnosis of an enlarged gland appears to be, the greatest difficulty is sometimes encountered to differentiate between such a gland and an inflammatory mass.

Diagnosis is furthered by observing the location of the enlargement and noting whether it is confined to one area or is diffuse, also whether it is confined to the external surface of the body or is present both externally and internally. The shape, size, and whether or not the skin is freely movable over the mass are other important criteria. The skin over an enlarged gland is usually freely movable, although this is not always the case and, moreover, the mobility of the skin over the gland may not be alike over all the glands. When the glands are imbedded between tense musculature, for instance, the overlying skin can hardly be separated from the gland and a similar condition exists with regard to glands in the parotid region at the angle of the jaw, over the sternocleidomastoid, and occasionally glands on top of the mastoid process.

Regarding location, if the swelling is in the neck, in the inguinal, or in the axillary regions, it is reasonable to assume *a priori* that it is an enlarged gland. On the other hand, if the mass is on the back of the chest or on the thigh, for example, it is undoubtedly some other kind of tumefaction.

With respect to shape, the gland is round and has a definitely outlined border but tumefaction due to inflammation has no free border, and, unlike the gland, becomes more shapeless the larger it grows. Of course, if a gland is surrounded by inflammatory tissue it may become an ill-defined mass. If several glands mat together and become attached to the underlying structures, biopsy study may be necessary before a diagnosis is possible.

In one of our cases, there was a painful swelling in the supraclavicular area. The overlying skin was inflamed, and our impression was that the swelling was an inflamed tuberculous gland. Operation revealed the swelling to be a cervical rib.

Naegeli<sup>8</sup> quotes two cases of a hard swelling in the middle of the neck mistaken for an enlarged gland that was actually a direct continuation of a carcinoma of the sinus of Valsalva.

Occasionally, an enlarged lobe of the thyroid, lying considerably outside the median line, is mistaken for a gland. If the patient is watched while swallowing, the swelling will move upward with deglutition if due to a thyroid lobe.

An inflamed, irritable inguinal hernia is sometimes mistaken for an enlarged gland. History will prove most helpful. If the patient states that a preexisting swelling that is greater on standing or coughing has suddenly become painful and is causing gastro-intestinal symptoms of nausea and vomiting, inguinal hernia is to be considered. Careful examination of the inguinal ring will usually clinch the diagnosis.

#### I. ADENOPATHY SECONDARY TO LOCAL INFECTION

Glandular enlargement secondary to local infection is usually inflammatory in nature, the enlarged glands generally being adjacent the seat of infection, though, more rarely, the

nearby glands are spared while the glands a distance away are affected. This is illustrated by an infection of the finger where the epitrochlear glands may be spared and the axillary glands enlarged. The primary infection need not be severe to cause adjacent glandular enlargement. It may have been of such a mild nature that the patient cannot recall it.

The fate of the gland depends on the virulence of the micro-organism. Certain micro-organisms, such as the streptococcus, staphylococcus, and gas bacillus, have more tendency to produce suppuration than others. On the other hand, the gonococcus, although causing local suppuration, will not bring about suppuration in adjacent glands.

Wherever localized infection takes place the lymph from the infected area drains toxins or bacteria into the adjacent gland and causes inflammatory changes in that gland. Generally, the gland becomes moderately enlarged and slightly tender, the enlargement diminishing with the subsidence of the primary infection although never so fully as to bring the gland back to its original size. This explains why most of us, inasmuch as every human being from childhood to any part of life has gone through some infection in some part of the body, have palpably demonstrable glands in the axillary, inguinal and cervical regions and perhaps, also, in the thorax and abdomen.

Occasionally, the virulence of the micro-organism is such as to cause suppuration and complete destruction of the gland, or a number of glands may coalesce and suppurate. Again, following the healing of the gland originally infected, adjacent or distant glands suppurate so that there is multiple glandular suppuration.

The thoracic and intra abdominal glands, although frequently enlarged secondary to local infection, rarely suppurate.

It is important to remember that, even though a lymph gland is the seat of chronic suppuration, it rarely serves as a focus of general sepsis unless the infected focus communicates directly with a vein.

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It is a very remarkable clinical fact that localized infec

tion with involvement of adjacent glands, whether leading to suppuration or not, are usually prognostically more favorable than infections which do not give rise to enlarged regional glands. For example, in pelvic cellulitis causing pelvic adenitis and enlargement of the inguinal glands, the primary symptoms are most severe and there is considerable systemic reaction, but the patients usually recover under appropriate care. This is generally true, also, of streptococcic sore throat with involvement, and even suppuration, of the cervical glands. On the other hand, pelvic vein infection or infection of the veins of the neck, giving rise to no glandular enlargement, usually terminates fatally unless the infected veins are accessible to surgical ligation.

**Adenopathy Secondary to Eczema**—Children subject to eczema often have glandular enlargement in the vicinity of the skin lesion. At one time eczema was considered to be secondary to the glandular enlargement, and such a child was classed as a status lymphaticus. Czerny has definitely shown, however, that most of these children have an exudative diathesis, not inherent in the child but due to faulty nutrition, over-feeding with milk being responsible, secondary to which there is glandular enlargement.

**Adenopathy Secondary to Favus**—Enlargement with suppuration of the glands in the neck, particularly of the posterior cervical glands, and sometimes, also, of the lacrimal, supra-orbital, and the submaxillary glands may occur secondary to favus. Fortunately, this is a condition that hygiene is completely eradicating, but in Vienna, after the war, we saw many cases where most of the glands of the neck and even the lacrimal glands continued to be enlarged long after the favus had disappeared.

## II. ADENOPATHY SECONDARY TO SYSTEMIC INFECTION

**Scarlet Fever**—Glandular enlargement, although secondary to many infections, is most conspicuous in the exanthematous diseases, particularly in scarlet fever and rubella. In scarlet fever, the cervical and inframaxillary glands are en-

larged in proportion to the severity of the infection of the nasopharynx and tonsils. The glands are painful and tend to coalesce, suppurating in some cases. If the mastoid bone is involved, the glands in that region, also, are enlarged and painful.

**Rubella.**—In rubella, or German measles, the cervical and inframaxillary glands are characteristically enlarged out of proportion to the infection in the mouth. The glands are not painful and suppuration never takes place.

**Tularemia**—There is a definite glandular type of tularemia in which the glands in the vicinity of the primary infection are enlarged. They are usually the axillary and epitrochlear glands, although, occasionally, the intra abdominal glands are involved, becoming of sufficient size to cause abdominal pain.

**Anthrax.**—As soon as the local infection on the lip or nose occurs, the inframaxillary and cervical glands become enlarged and exceedingly painful. The glandular enlargement is out of proportion to the focus of infection. This is emphasized because if the anthrax infection is recognized at this period and excised at once, followed by serum treatment, the life of the patient may be saved. If the anthrax lesion develops into prominence, however, which happens within two or three days, irrespective of what is done for the patient the outcome is fatal. If the patient is cured of his anthrax, the glands usually subside, although under rare conditions they may suppurate with anthrax bacilli present in the pus.

**Rheumatic Fever**—In some cases of rheumatic fever, the intra abdominal glands enlarge, causing severe abdominal pain and transient lymphocytosis. If the articular symptoms and manifestations are not outspoken, the condition may be mistaken for a surgical abdominal disease. In the vast majority of cases where the abdominal pains are severe in rheumatic fever there is a history of tonsillar involvement preceding the abdominal symptoms. Nose bleed is present more often than in typhoid. There is a moderate leukocytosis but a normal polymorphonuclear count. In all cases, as was



shown in our hospital by Dr Arthur M Weiss,<sup>9</sup> the sedimentation rate is increased, even more than in many other acute infections

It is important to differentiate enlarged glands due to rheumatic fever, particularly those with abdominal symptoms, because they are favorably influenced by rectally administered sodium salicylate, 80 in 2 ounces of normal saline solution, to be retained, twice or three times daily. Each medicated enema should be preceded by a fairly warm soapsuds cleansing enema to aid the absorption of the drug. If the patient cannot retain the enema,  $\frac{1}{2}$  teaspoonful of paregoric should be added.

**Anterior Poliomyelitis**—It is a striking fact that abdominal symptoms due to enlarged intra-abdominal glands often are in the foreground for the first few days of anterior poliomyelitis. These pains are usually attributed to the general hyperesthesia that exists in poliomyelitis, if they are due to enlarged intra-abdominal glands there is moderate abdominal rigidity, in contradistinction to the marked relaxation and flaccidity of the abdominal muscle when the cause of the abdominal pains is spinal nerve involvement.

Most authors, including Matthes,<sup>10</sup> call attention to the fact that, although moderate leukocytosis and polymorphonucleosis make differential diagnosis difficult, perspiration is an outstanding feature during the early stage of poliomyelitis and is often a leading sign. Therefore, if abdominal pains are present in association with very marked perspiration, even without other symptoms of poliomyelitis, surgical disease of the abdomen is ruled out.

**Typhoid Fever**—Invasion of the lymphatic system is characteristic of typhoid fever, which is nearly always accompanied by enlarged intra-abdominal glands, particularly in the ileocecal region, and especially during the first two weeks of the disease. An erroneous diagnosis of appendicitis is not uncommon because of the right-sided pain caused by these enlarged glands. If a blood examination is made, however, a mistaken diagnosis is impossible, for, even during the early period of typhoid fever, leukopenia and lymphocytosis are in-

variably present unless there is a mixed infection of the glands with involvement of adjacent viscera. In that event, and particularly if the glands suppurate, the blood picture changes from lymphocytosis to polymorphonucleosis unless the supuration of the glands is directly due to the typhoid bacillus, in which event the lymphocytosis persists.

**Primary Infectious Lymphadenitis of the Mesenteric Glands**—Occasionally, the enlargement of the abdominal glands is confined to the mesenteric glands, giving rise to a diffuse lymphadenitis. In the vast majority of cases, this occurs in children, and is undoubtedly secondary to general intestinal infection. It is characterized by severe abdominal pain and by diarrhea or constipation. Very often, it is associated with tonsillitis and enlargement of the glands in the neck. There is no increase in lymphocytes so that the clinical picture is most difficult of interpretation, the condition being often mistaken for appendicitis.

A case in the adult is sometimes encountered. The disease begins with violent general abdominal pain which later localizes over the right side of the abdomen. There is a moderately elevated temperature ( $101^{\circ}$ – $102^{\circ}$  F) and the blood findings are a moderate leukocytosis and an increase in the polymorphonuclears. We recently encountered such a case which we were misled to diagnose acute appendicitis. Operation proved it to be lymphadenitis of the mesenteric glands, the most enlarged glands being those in the ileocecal region. The prognosis in these cases is usually good. Remarkably enough, in our case, after the operation, although nothing was done by the surgeon except to establish diagnosis, the temperature subsided and the patient recovered entirely within a few days.

**Adenopathy Secondary to Tuberculosis**—Tuberculous adenopathy is generally confined to one group of glands. The superficial glands most often affected are the cervical and submaxillary, rarely the axillary, and still more rarely the inguinal glands. The thoracic glands most often involved are those in the hilum, less frequently in the mediastinum. The mesenteric glands may be tuberculous and, occasionally, one encounters a

case of diffuse enlargement, including nearly all the superficial and some of the internal glands

*Tuberculous Superficial Glands*—Tuberculous glands in the neck are generally secondary to tuberculous infection of the tonsils, occurring most often during the first year of life. In fact, it is essential to realize that whenever, during the first year of life, there is a persistent ulcerative tonsillitis, the infection is undoubtedly of a tuberculous nature for both the infectious type of tonsillitis and diphtheria are rare before the second year. In the vast majority of cases, the invader is the bovine type of tubercle bacilli.

The clinical characteristics of tuberculous superficial glands are: A tendency to coalesce, tenderness to touch, and an adherent overlying skin with the center of the gland so retracted as to present local umbilication.

The fate of the gland depends on the degree of tuberculous invasion. Herring and Macnaughton<sup>11</sup> have shown, experimentally, that when only a small number of moderately virulent tubercle bacilli invade the gland, a marked lymphocytic reaction takes place in the corticomedullary portion, the lymphocytes forming a barrier to prevent the spread of the infection. The endothelial structures are but slightly invaded, although there is some reaction on the part of the reticulum so that connective tissue forms and epithelioid cells are present. Lime is not deposited and there is no caseation.

If a large number of tubercle bacilli invade the gland, both the corticomedullary and the reticulo-endothelial portions are involved. There is distortion of the endothelium by giant cells and the influx of polymorphonuclears leads to suppuration with degenerative changes. It is highly important to remember that suppuration is a factor only in tuberculous superficial glands, the thoracic and intra-abdominal glands seldom suppurating.

Enlargement of the inguinal glands may result from unhygienically practiced ritual circumcision. Cases have been reported, also, where gluteal injection of convalescent serum for measles containing tubercle bacilli led to tuberculous in-

ginal glands In previous years, when superficial tuberculous glands were frequent, the breaking down of these glands and invasion of the surrounding skin led to deformative scars on the face and other parts of the body, this condition being known as scrofula.

In the majority of cases of tuberculous enlargement of the superficial glands, without suppuration, there are few systemic symptoms The patient is generally of the asthenic type, tiring readily and having a capricious appetite. If the glands suppurate, the local pain is severe and the systemic symptoms are somewhat outspoken

When a single group of glands is enlarged and painful, the ideal treatment is local excision On the other hand, if a large number of superficial glands are involved, heliotherapy is the treatment of choice  $\alpha$  Ray therapy is beneficial in some cases Fresh air and food, qualitatively and vitamin rich, are, of course, essential If there is evidence of secondary anemia, iron and arsenic by mouth (0.3 reduced iron three times a day or Fowler's solution 1 to 5 drops three times a day) are very helpful

*Tuberculous Thoracic Glands*—Tuberculous thoracic glands occur most often in childhood, sometimes as early as the fourth or fifth year, the entrance of infection being through the respiratory tract The systemic symptoms are mild, consisting of moderate elevation of temperature, loss of appetite, marked irritability, and pallor without anemia, in other words, the patient is the "weak, irritable child" The condition is usually regarded lightly and diagnosed as recurrent grippe or bronchitis

If the glands press on the trachea, as they often do, there is expiratory difficulty, if on the larynx, there is hoarseness and inspiratory stridor When there is an acute infection of the thoracic glands, the supraclavicular glands, also, may be involved Occasionally, the infection spreads to the tonsils, causing tuberculous tonsillitis and danger of a further spread to the digestive tract

The  $\alpha$  ray signs are meager because the glands are too

soft to cast a shadow, unless they press on the bronchi, in which case there is a dense shadow in the adjacent lung due to atelectasis

The most important diagnostic clue is furnished by the von Pirquet test, a positive reaction, at this early age, is absolutely indicative of tuberculous infection. If there are enlarged glands in the back of the chest, pressing on the bronchi or trachea, and the child can be made to count, the d'Espine sign is helpful, the child whispers "99" or "1, 2, 3," and if enlarged glands press on the bronchi the whisper fremitus will be heard as far down as the second or third dorsal vertebra. Ordinarily this fremitus disappears at the fifth or sixth cervical vertebra. Another diagnostic sign is the Smith sign, that is, if glands press on the subclavian artery, on auscultation over the right infraclavicular region, with the head bent backward, a harsh bruit will be heard.

As a rule, the tuberculous infection subsides and perfect healing takes place. Some of the glands may retrogress to a large extent, while others may continue to be small, round, calcified glands that give rise to no symptoms. In view of the fact, however, that the gland entombs living bacilli which may escape if it breaks down, it has pathologic significance. Such a breakdown may cause severe pulmonary or generalized tuberculosis. Cases have been reported where pneumonia with pleurisy at the site of the gland caused the gland to break down and lead to secondary tuberculosis—the bronchopneumonia that eventually passes into pulmonary tuberculosis. In other cases, trauma at the site of the gland near the pleura has caused traumatic or tuberculous pleurisy. Sometimes, without known cause, tuberculous pleurisy develops at the location of the gland.

If a mixed infection with suppuration of the glands takes place and the glands break down, fatal suppurative mediastinitis may ensue.

Cases have been reported, too, where tuberculous glands near the pericardium have led to tuberculous pericarditis with Pick's cirrhosis. More rarely, suppuration of tuberculous glands

spreads to the spinal vertebrae causing tuberculous spondylitis of the upper dorsal or cervical vertebrae with deformity (gibbus back)

*Tuberculous Intra-abdominal Glands*—Tuberculosis of the intra abdominal lymph glands is very rare but is still encountered occasionally in an acute, more often in a chronic form Gibson<sup>1</sup> found x-ray evidence of calcified tuberculous abdominal lymph glands in 19 out of 200 children The acute form in children is known as *tabes mesaraica*

Infection of the intra abdominal glands is usually the result of tuberculosis of the intestines The primary lesion often heals completely, but the glands, which attain the size of a walnut and are accessible to palpation, remain enlarged If situated in the ileocecal region they may cause localized pain and, being tender, may be mistaken for appendicular abscess Occasionally these intra abdominal glands mat together to form a large tumor mass, simulating abdominal lymphosarcoma or some other form of mesenteric tumor A case of this nature was encountered by us Exploratory operation was advised because of the hard intra abdominal tumor mass, but the patient refused Under the impression that the condition was lymphosarcoma we advised x ray treatment which was without favorable influence We then considered the possibility of tuberculous adenopathy and advised heliotherapy and other hygienic measures, the result being complete disappearance of the glands It has been eight years since the patient received this treatment, during which time no masses have been palpable and the only complaint of the patient is occasional abdominal discomfort, most likely due to the adhesions that so often form as a result of chronic mesenteric glands

It is important to differentiate intra abdominal tuberculous glands from inflammatory mesenteric glands The gastrointestinal tract is frequently subject to minor infections so that the small glands in the vicinity of the affected organ become calcified in the course of time If small, they give rise to no symptoms unless situated in the right hypochondrium or ileo-

cecal region, when they may simulate biliary or gallbladder disease, appendicitis, or, in women, adnexal disease. Heliotherapy is of no avail in these cases, operative removal of the glands being the only cure. Inflammatory glands are not accessible to palpation, as are tuberculous intra-abdominal glands.

Occasionally, tuberculous mesenteric glands give rise, by way of the lymphatics, to a psoas abscess and tuberculosis of the lower spine, sometimes to hip disease. In women, the tubes and ovaries may become invaded as the result of breakdown of tuberculous pelvic glands and some authors have attributed the sudden appearance of an ischiorectal abscess to the breaking down of a tuberculous gland in the pelvis.

*Tabes Mesaraica*—In this acute form of tuberculous mesenteric glands in children, the systemic symptoms are more pronounced than intra-abdominal pressure symptoms. They are Extreme weakness, a protracted subfebrile course, diarrhea with excessively fatty stools, extreme emaciation, and secondary anemia. The glands on the right side are more often enlarged than those on the left, giving rise to pain in the ileocecal region or right hypochondrium and simulating appendicitis or gallbladder disease. Most of the glands are soft, but some are calcified. It is important to differentiate *tabes mesaraica* from Herter's disease, which is a nonspecific glandular infection in children accompanied by diarrhea and fatty stools but in which the glands are so soft as not to give rise to pain or roentgenological signs. As a rule, *tabes mesaraica* terminates fatally. In some cases, however, the acute adenopathy is extremely mild with most of the intra-abdominal glands becoming calcified and giving rise, later in life, to symptoms if, by virtue of size, they cause pressure on, or, by connective tissue formation, have become adherent to neighboring organs.

*Diffuse Tuberculous Lymphoma*—A very rare type of tuberculous adenopathy is diffuse tuberculous lymphoma which, in the majority of cases, is of hematogenous nature. Practically all of the superficial glands and, to a certain extent, the

mediastinal and mesenteric glands are involved. They achieve the size of a hazelnut or peanut, are not painful and are discrete. The overlying skin is freely movable. There are few systemic symptoms. Only by a biopsy can the nature of the disease be ascertained.

One of our patients was a male, forty five years of age, who was admitted to Beth Israel Hospital, on the service of Dr M. A. Rothschild, with secondary anemia, vague abdominal pain, and glandular enlargement wherever glands are



Fig. 82.—x Ray of chest showing tuberculous lymphangitis of the lungs in a case of tuberculous lymphoma

normally present. In addition, there were newly formed glands around the mamilla and over the entire posterior aspect of the chest (Fig. 82). The glands were discrete, nonumbilicated, and the overlying skin was freely movable. Clinically, the condition resembled lymphosarcoma, but pathologic examination of an excised gland proved it to be tuberculous lymphoma (Fig. 83). The patient left the hospital after a few weeks, unimproved, despite quartz lamp treatment, iron and arsenic. The fate of these patients is eventually to die of exhaustion as in sarcomatous adenopathy and in Hodgkin's disease.



**Luetic Glands**—Enlargement of the glands due to syphilis occurs chiefly during the first and second stages of lues

*During the first stage of lues* it is exceedingly rare for glands other than those near the primary lesion to be affected. The inguinal glands are most often enlarged, secondary to a primary lesion in the genital organs. The enlargement is generally bilateral, the overlying skin is not inflamed and is freely movable, and the glands feel doughy or like an air cushion. They are only slightly tender and tend to coalesce, but so

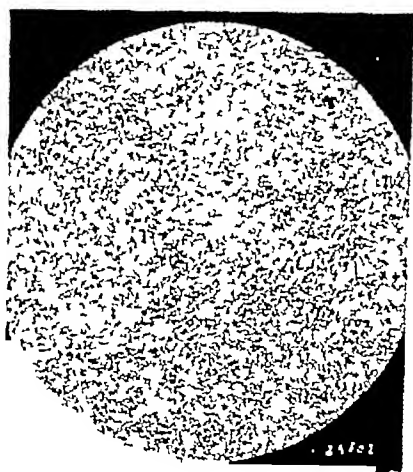


Fig 83—Biopsy of gland from the case of tuberculous lymphoma presenting epithelioid cells and Langhans' giant cells. Necrosis and caseation absent.

seldom suppurate that this is a differential point between enlarged inguinal glands due to lues and enlargement secondary to chancroid. Suppuration may occur, of course, if treatment is by irritating salves or extreme heat. Anal or cervical chancre, also, may cause pelvic adenitis with suppuration and suppuration sometimes occurs in glandular enlargement secondary to lip or tongue chancre, these regions are rich in bacteria so that a mixed infection by pus-producing organisms sometimes takes place.

The cervical and submaxillary glands are involved only

when the primary chancre is on the lip or tongue. They are not markedly enlarged or tender, unless there is a large submaxillary gland which may become exceedingly painful, and are discrete.

If unexplained large axillary or epitrochlear glands are found unilaterally, during the first stage of lues, one should inspect the patient's fingers for evidence of a primary lesion. One of our patients was a nurse who ran an unexplained temperature with ulceration of the throat that would not yield to ordinary treatment. She was treated for a long time on an indefinite basis. Then enlargement of the right epitrochlear and axillary glands awakened the suspicion of lues. Careful examination by a dermatologist (this was before the Wassermann era) revealed a small, brownish scar on the right index finger. A diagnosis of glandular enlargement due to lues was made and proper therapeutics successfully instituted.

Epitrochlear glandular enlargement has a tendency to persist throughout life, and is a most important diagnostic phenomenon of syphilis. However, it should not stamp an individual as luetic, permanent epitrochlear enlargement is found, also, in those who were afflicted in infancy with Barlow's disease with periosteal infection of the elbow joint, or in childhood were rachitic. A positive Wassermann reaction is, of course, absolutely diagnostic.

*During the second stage*, the cervical glands are most often enlarged due to the throat, pharynx, tonsillar, or mouth infection that characterizes this stage of lues. In some cases, marked by widespread exanthematous eruptions, there is diffuse enlargement of the superficial glands. The glands are generally discrete, only slightly enlarged, and moderately tender. Suppuration rarely occurs. The temperature is elevated and there is considerable lymphocytosis.

Under antiluetic treatment the glands will recede considerably in size.

**Chancroid.**—Glandular enlargement secondary to chancroid, which is always extragenital, is confined to the inguinal glands. The glands coalesce, are inflamed, the overlying skin

is red and adherent, and even when the glands do not suppurate they are exceedingly tender. In the vast majority of cases the glands suppurate.

**Lymphogranuloma Inguinale**—In this condition, which is due to a filterable virus, there may be a primary lesion of the type of papule, pustule, herpetic process, or of a specific urethritis, which is sometimes confused with gonorrhea. Following the primary lesion, which is generally evanescent in character, there is an involvement of the draining lymph nodes. The adenitis of lymphogranuloma inguinale is characteristic. The nodes in a chain become fused together in a large mass, which may reach the size of a lemon, and then the process breaks down with multiple fistulous openings. Along with the local adenitis, there may be systemic symptoms of malaise, loss of appetite, loss of weight, rheumatic symptoms, eruptions on the skin, and an elevation of temperature. Occasionally the high temperature persists over a long period, successive flare-ups accompanying the involvement of fresh lymph nodes.

The picture is somewhat different in the female, owing to the fact that most of the lymph channels running from the vulva drain into the nodes around the lower part of the rectum, with the result that there is an inflammatory reaction of these nodes and a secondary involvement of the rectal wall. Later there may be an inflammatory stricture of the lower rectal walls, annular or tubular in character. Very rarely, excrescences develop around the anal orifice, sometimes accompanied by fistulas, and there may be a certain amount of elephantiasis of the vulva and fistula formation.

The Frei test<sup>13</sup> is helpful in making the diagnosis. This test, which has been confirmed by Bloom,<sup>14</sup> is a specific intradermal test performed as one would make a tuberculin test. The antigen consists of some of the sterilized pus taken from a bubo just before it is going to break down, but not pus from the patient to be tested. One-tenth cc of this material is injected intradermally, and in forty-eight hours there will be a raised, erythematous tubercle from 0.5 to 1 cm in diameter in a positive case.

Antimony is the best preparation for treatment. Injections of fuadin are given intramuscularly one in two or three days, starting with a dose of 2 cc. and working up to a maximum dose of 5 cc., a total of from 45 to 50 cc. of the preparation being given, which constitutes a course. If necessary, the course is to be repeated within a month. Rest in bed is essential, and minor surgical procedure, such as opening necrosing lymph nodes or partial removal of a broken down lymph node may be necessary.

### III. ADENOPATHY AFFECTING PRIMARILY THE CORTICOMEDULLARY PORTION OF THE LYMPH GLAND

Returning to our classification of adenopathies that affect chiefly the corticomedullary or the reticulo-endothelial portion of the gland, we have in the former group, first, adenopathy with an overproduction of mature lymphocytes represented by Pfeiffer's glandular fever, secondly, lymphatic leukemia, in which the corticomedullary portion returns to its embryonal function, producing only immature lymphocytes, thirdly, follicular lymphoblastoma, in which a more abnormal type of lymphocyte is produced, and, fourthly, lymphosarcoma, characterized by the formation first in the corticomedullary portion of the gland of a new, malignant cell.

**Pfeiffer's Glandular Fever**—In 1888, Pfeiffer described a disease in children beginning as an infection of the tonsils, pharynx, and often of the mouth, but unaccompanied by any hemorrhagic diathesis. The temperature is elevated and stomatitis is present in some cases. Most of the cervical and submaxillary glands, often the axillary and inguinal, and sometimes the epitrochlear glands are enlarged. The spleen is almost invariably enlarged. The glands are discrete, do not coalesce, are not tender, and the overlying skin is freely movable. The glands never suppurate.

The enlarged spleen and the diffuse enlargement of the glands, in conjunction with a marked lymphocytosis (60 to 90 per cent), make the disease simulate lymphatic leukemia, but the following findings in the blood will differentiate it. The lymphocytes are mature, the blood platelets are not in

creased in number, and no other blood elements are affected except the polymorphonuclears which are numerically reduced. Eosinophils are conspicuously absent throughout.

Cases have been reported where excision of the gland has shown a definite crowding of lymphocytes in the corticomedullary portion without any other change in the capsule or reticulo-endothelial portion of the gland, demonstrating that it is an overfunctioning of the corticomedullary portion and of the lymph follicles of the spleen which is responsible for the glandular and splenic enlargement.

The cause of Pfeiffer's glandular fever is unknown. It is confused by many with infectious mononucleosis, but we regard these as two very distinct entities for reasons that will be stated in the discussion of the latter condition.

The course of Pfeiffer's glandular fever is protracted, lasting weeks or months, but the termination is favorable.

**Lymphatic Leukemia**—In both the acute and chronic form, lymphatic leukemia is characterized by qualitative and quantitative changes in the lymphocytes, immature lymphocytes being produced in extremely large numbers. Even new lymph glands that form produce immature lymphocytes.

*Acute* lymphatic leukemia occurs most often in young children or early in puberty, although it may develop at any age. It commences with an infection of the tonsils, pharynx or nose, which is followed soon by hemorrhagic diathesis manifesting itself in bleeding from the nose and gums, ecchymosis, and petechiae, the patient succumbing within one to three weeks. The temperature is invariably elevated and may become septic in type so that the condition is mistaken for septicemia. If the blood is not examined, the diagnosis may be streptococcal sore throat, diphtheria, or Vincent's angina because the smear shows fusiform bacilli which, in reality, are secondary invaders. The glands of the neck are only slightly affected, but the inguinal, axillary and epitrochlear glands are considerably enlarged, and the spleen is always enlarged. All of the glands, including those of immense size, are freely movable and not tender. They do not coalesce or suppurate.

The blood examination reveals an invariable increase in white cells, sometimes to a quarter of a million but more often to between 80,000 and 100,000, marked lymphocytosis (80 to 90 per cent) characterized by large, immature lymphocytes, and polymorphonuclear cells likewise predominantly immature. In some cases, there are 5 to 10 per cent myeloblasts and myelocytes. Eosinophils are conspicuously absent. The blood platelets are considerably reduced, as are the red blood cells which show evidence of poikilocytosis and anisocytosis. In other words, the entire hematopoietic apparatus is involved.

In rare cases, the leukocytes are not numerically increased but diminished, abnormal lymphocytes constituting the characteristic expression of the disease. These cases of subleukemic leukemia are differentiated with such difficulty that unless a most thorough examination of the blood is made, the diagnosis may be thrombocytopenic purpura.

Differentiation between subleukemic lymphatic leukemia and thrombocytopenia is of the utmost importance because in the latter condition removal of the spleen is generally a life-saving therapeutic agent. The most important clinical differential point is that in thrombocytopenia, if the spleen is enlarged at all, it is only moderately increased in size while the superficial glands are not enlarged to any degree. Moreover, in thrombocytopenia, hemorrhagic diathesis is the most noticeable sign, very often in the form of purpuric spots over the extremities, with profuse bleeding from the uterus at the time when menstruation begins or during the menopause. As the disease progresses, there is bleeding from the mouth and gums, also. There is rarely a diminution of white cells in contradistinction to subleukemic leukemia when they may drop to 1000 or 2000 only, with the polymorphonuclear cells showing little change except for an occasional degenerated cell. The predominance of large, immature lymphocytes is, of course, positively indicative of lymphatic leukemia.

*Chronic lymphatic leukemia* is more common than the acute form, and is extremely rare in children. It is so insidious in onset that it cannot be traced as a consequence of acute lym-

phatic leukemia The patient generally consults a physician because of gradually progressive weakness, loss of appetite, and enlargement of the cervical and submaxillary glands Hemorrhagic diathesis is not pronounced, although the patient may bleed moderately from the nose There is no great tendency to ecchymosis, even after trauma, and petechiae are very rare The physical appearance of the patient is that of secondary anemia, with a greenish tinge of the sclera In most cases of chronic leukemia, there is lymphocytic infiltration of the liver, and in advanced cases there may be lymphatic infiltration into practically every organ of the body

The severity of the disease is proportionate to the extent of enlargement of the external glands, that is, the more widespread the enlargement, the more rapid the progress of the disease Each gland may grow to an immense size, the glands in the neck, axilla and inguinal region sometimes becoming as large as an orange The glands in the mammary region, as well as the newly formed superficial glands, however, are smaller All the glands are freely movable, not tender, do not coalesce, and, as a rule, do not suppurate An exceptional case that we have encountered was one in whom there was spontaneous suppuration of a gland in the thigh

The mediastinal glands are only moderately enlarged, never to a degree to cause pressure symptoms, which differentiates this condition from lymphosarcoma Mediastinal glands are demonstrated on the postmortem table far more often than clinically As they are not calcified they do not cast a shadow when examined roentgenographically

The intra-abdominal glands, although somewhat involved and numerically increased, are seldom sufficiently large to cause severe pressure symptoms The spleen is invariably enlarged, though not to the degree accompanying myeloblastic leukemia If the glands in the hepatic region, particularly those around the ducts, do enlarge, they press on the common duct and on the papilla vateri and cause such profound jaundice that if the blood is not examined an unnecessary operation may be performed

A case of this nature was seen by us through the courtesy of Dr L. Greenwald. The patient was a man, forty years of age, who was entirely well until, suddenly, he began to experience pain in the right upper quadrant with radiation to the right shoulder. This was accompanied by progressive jaundice. Physical examination revealed marked resistance in the right upper quadrant and a definite tumor mass in the right hypochondrium which was interpreted as enlargement of the right lobe of the liver and gallbladder due to a carcinoma of the head of the pancreas. An examination of the blood proved the condition to be chronic lymphatic leukemia. The patient died within a few weeks as a result of cholemia. Remarkably enough, none of the external glands was ever sufficiently enlarged to give a clue to the diagnosis. An autopsy was not permitted and so we do not know whether or not other intra-abdominal and intrathoracic glands were involved.

The most important diagnostic clue is furnished by the blood examination. The leukocytes and the lymphocytes, which are large and immature, are almost invariably increased in number. The increase in lymphocytes varies, however, at one time, they may number 200,000, and, at another, only 30,000 or 40,000. The other elements of the blood are altered according to the severity of the disease. In the milder cases, there are 3,000,000 to 4,000,000 red blood cells, in the more severe cases, only 2,000,000. There is no poikilocytosis or anisocytosis. The hemoglobin is always reduced, the color index falling to 0.7 or 0.6. The blood platelets are reduced, but only to 80,000 to 150,000. Myeloblasts are seldom seen, although occasionally 6 to 10 per cent are present, transiently. If the pathologist has difficulty in differentiating large, unripe myelocytes from myeloblasts, the oxydase reaction provides a clue, being positive for myeloblasts and negative for myelocytes. Recently, the heterophilic reaction (Paul Bunnell test<sup>15</sup>) was introduced by Alan Bernstein<sup>16</sup> as a diagnostic aid, in leukemia the lowest titer of heterophilia is present, in contradistinction to the high titer of infections mononucleosis.

Remissions in the blood picture, as in the clinical symp-



toms, are not unusual, but it is our experience—and this was often emphasized by Pappenheim—that once a malignant hematopoietic affection always one. Therefore, if the blood is examined carefully, even during a remission, some degree of secondary anemia will be noticed as well as the presence of a certain percentage of medium and large immature lymphocytes.

It is important to remember that an intermittent infection may convert the blood picture of lymphatic leukemia into a normal one, or one of an acute infection. This is true particularly when there is an intervening pneumonia, as we have had occasion to observe<sup>17</sup>. The patient was a woman in her late forties, who entered Beth Israel Hospital three times in two years, suffering each admission from bronchopneumonia. During these attacks her leukemic blood picture was entirely supplanted by one of a moderate infection—8000 leukocytes and 80 per cent polymorphonuclears. Several weeks after recovery from the bronchopneumonia, the blood picture of chronic leukemia would reappear.

As a rule, an intercurrent infection hastens the end in chronic lymphatic leukemia. Another of our patients walked around for a long time with enlarged submaxillary and cervical glands, to which he paid no attention. When we first saw him, it was in his home where he was suffering from an acute febrile disease, probably grippe. Blood examination showed that he also had some subleukemic leukemia. Within three days he died of the intercurrent infection, the terminal symptoms being those of pulmonary edema although on the day before death he had very few lung signs. That this sudden attack was not an exacerbation of the leukemia was evidenced by the fact that there was neither symptom nor sign of hemorrhagic diathesis.

In many cases of lymphatic leukemia there are spontaneous remissions, cases having been reported where the disease has lasted, with such remissions, from three to twelve years. We had one patient who lived fifteen years. x-Ray treatment has a very favorable influence on the disease proper.

and the administration of arsenic in the form of Fowler's solution in ascending doses beginning with 2 drops three times a day and ascending gradually to 10 drops three times a day, then descending to 2 drops followed by a month without its administration before repeating the course, is likewise beneficial. If cacodylate of soda is preferred to Fowler's solution, it should be given intramuscularly once a day, beginning with 0.05 until 0.5 is gradually reached. If there is an increased basal metabolism, Lugol's solution may be attempted, 5 drops three times a day. Blumgart<sup>18</sup> and his associates have recently advocated and have actually carried out ablation of the thyroid in some of these cases.

**Follicular Lymphoblastoma.**—Among the diffuse adenopathies, one that offers the greatest difficulty in diagnosis, not only for the clinicians but for the pathologist, is follicular lymphoblastoma.

The disease was first described by Baehr<sup>19</sup> as lymphoma, a name that was changed later by Brill, Baehr and Rosenthal<sup>20</sup> to follicular lymphoblastoma as a result of observing and studying several cases very carefully. These authors found that the enlargement of the lymph gland is due to the presence in the gland of an enormous number of abnormally large lymph follicles resembling gigantic germinal centers, which overlap each other and compress the intervening sinuses. These pathologic findings have been confirmed by Symmers.<sup>1</sup>

The clinical picture is one of generalized lymphadenopathy, including enlargement of the spleen which may reach the size of the spleen in Gaucher's disease or in myeloid leukemia. Giant lymph follicles are not as numerous in the spleen, however, as in the glands, the spleen being studded by large malpighian bodies.

Of the superficial glands, those generally most involved are the cervical, inguinal and axillary glands. They vary in size, remain discrete, and do not break through into neighboring tissues. The lacrimal and mammary glands are sometimes invaded. The process may even include the subcutaneous fat and the fat tissues of the orbit, pressure in the orbit causing exophthalmos in one of Baehr's cases.

If the mediastinal or intra-abdominal lymph glands are invaded, the glands coalesce, particularly in the latter stages of the disease

An important characteristic of follicular lymphoblastoma is that so long as the intra-abdominal and intrathoracic glands are not affected, the patient is fairly comfortable and has but slight anemia

The blood picture is not characteristic except for a terminal secondary anemia. If the spleen is very much enlarged, the blood picture is characteristic of other splenomegalic diseases, presenting monocytosis and secondary anemia

The duration of the disease, according to Brill, Baehr and Rosenthal, is from one to fifteen years. The glands are extremely sensitive to radiation, as first pointed out by Baehr and reemphasized by Rosenthal, Harris and Kean,<sup>22</sup> and because of this ready response to treatment the disease was considered, at first, to be benign. However, time has shown that a recurrence always takes place, the condition terminating as lymphosarcoma. This termination as lymphosarcoma, however, does not minimize the importance of identifying the disease, early in its course, as a distinct entity, namely follicular lymphoblastoma, because it is well known that any diffuse benign adenopathy can change its pathologic character in the course of time

**Lymphosarcoma**—Lymphosarcoma, which Kundrat<sup>23</sup> was first to distinguish from other forms of adenopathy, originates in one group of lymph glands and spreads rapidly by way of the lymphatics to neighboring and distant glands and other organs. Very rarely, it begins in the tonsil, causing it to ulcerate

Once involved, the glands grow rapidly and, matting together, break through their capsules to infiltrate and destroy adjacent tissues and structures. In many instances, in contradistinction to lymphogranuloma, the lymph follicles of the intestines are also affected so that they ulcerate and bleed. In one of our cases, not only was there enlargement of all normally present superficial glands, but new superficial glands of varying

size were scattered all over the surface of the body, but particularly around the nipple, in the posterior aspect of the chest, and along the spinal vertebrae

The greatest size is attained by the glands in the mediastinum, neck and inguinal region, some becoming as large as an orange. The overlying skin is not adherent unless the glands are exceedingly large or mat together. There is rarely inflammation or suppuration except as the result of excessive roentgen treatment or external irritants

Symptoms due to pressure become marked very early in the course of the disease because of the tendency of the glands always to grow larger and never spontaneously to diminish and because in nearly all cases the mediastinal and less frequently the intra abdominal glands are involved. Cases are encountered where the patient makes his first appearance with terrific dyspnea, cyanosis, enlargement of the superficial veins of the chest and possibly also those of the neck, indicating pressure on the vena cava or subclavian vein, often swelling of both arms due to dilatation of the veins in the arms, and with marked dulness or flatness over the sternum and upper part of the chest. Despite the flatness, however, there is no evidence of hydrothorax.  $\alpha$  Ray examination reveals an immense, dense shadow within the upper part of the thorax, merging with the thoracic aorta, and most often occupying the mediastinum

A remarkable feature of these cases is their ready response to  $\alpha$  ray treatment. One or two  $\alpha$  ray treatments may give such relief to the patient that when he returns to the office he is practically a new person with roentgen examination showing marked diminution in the size of the glands or their actual disappearance

This rapid response of lymphosarcomatous glands to  $\alpha$  ray treatment is an indication that pathology in the lymphoid structures is responsible for their enlargement inasmuch as lymphoid tissue is exceedingly sensitive to the  $\alpha$  ray

The intra abdominal glands when invaded, do not grow so rapidly as to give rise to pressure symptoms but very often

they infiltrate the intra-abdominal digestive organs causing ulceration of the stomach or intestines and profuse bleeding. More rarely, one sees a case where the glands do not cause ulceration but give rise to obstruction. This can happen in any part of the intestines, but is most frequently encountered in the jejunum, as exemplified by a case that we saw recently through the courtesy of Dr Henry Greenfield. The patient was a young man in his early thirties, suffering from digestive disturbances and pain over the left side of the abdomen. There was a palpable, irregularly outlined tumor in the left hypochondrium which *x*-ray demonstrated to be a deformed jejunum (Fig 84). The condition was diagnosed as lymphosarcoma, confirming Dr Greenfield's first impression, and operation by Dr William Linder proved this to be correct. The patient made a rapid recovery from the operation, which was performed six months ago, and *x*-ray treatment since that time has enabled the patient to be very comfortable.

We vividly recall another case of intra-abdominal lymphosarcoma, a young nurse who suddenly developed pain in the upper abdomen accompanied by severe hematemesis. Until this catastrophe, she was actively engaged in the office of a very busy practitioner. Because of her age—she was in her twenties only—and the sudden onset of these symptoms, the possibility of lymphosarcoma invading the stomach was considered. She was sent to Mt Sinai Hospital for operation by Dr A A Berg. An almost complete gastrectomy was performed but she did not recover. Pathologic examination of the gastric tumor proved it to be a lymphosarcoma and at post-mortem other intra-abdominal lymphosarcomatous glands were discovered. This case, which could not have been totally asymptomatic throughout its course, illustrates particularly well the euphoria that is so typical of lymphosarcoma, and which is so strikingly different from the despondency that characterizes Hodgkin's disease.

Occasionally, lymphosarcoma invades the glands in the rectum so that they become large enough to be easily palpated by rectal digital examination. One case that we have seen was

a lawyer who, at the age of thirty, developed a very diffuse lymphosarcoma, including the glands in the rectum which became so large as to cause colonic obstruction. Under  $x$  ray treatment the glands diminished, including the rectal glands,



Fig 34—Defect of jejunum due to lymphosarcoma (confirmed by operation)  
(Dr Greenfield's case)

and the patient was able to continue his professional activity until within a very few weeks of his death, a year and a half ago at the age of thirty-eight.

More rarely the vaginal glands are involved, causing a large tumor in the vagina that may ulcerate, and still less fre

quently lymphosarcoma includes the osseous system or the cerebrospinal system. As a rule, however, when either of these systems is invaded, in conjunction with a generally lymphadenopathy, the disease is not lymphosarcoma but lymphogranuloma.

The systemic symptoms of lymphosarcoma are intermittent elevations of temperature and a progressive weakness. Strangely enough, the cachexia that is characteristic of other malignant diseases is seldom present.

The blood findings are those of secondary anemia. There is usually moderate leukocytosis and polymorphonucleosis, but if the bone marrow is involved there may be leukopenia or abnormal cells, simulating myelocytes, in percentage large enough to suggest the possibility of myeloid leukemia.

The outstanding feature of the pathologic picture is the homogeneous character of the cells in contradistinction to the heterogeneous cells in Hodgkin's disease. The architecture of the lymph node is replaced by a diffuse collection of round cells, consisting of small or large normal lymphocytes, and a more primitive cell resembling the myeloblast, with reticulum between the cells. In some cells, according to Boyd,<sup>24</sup> seven or eight erythrocytes are found.

Ewing<sup>25</sup> has described a special type of lymphosarcoma which is known as Ewing's reticulum cell sarcoma of the lymph nodes. It invades primarily and almost exclusively the reticulo-endothelium, and a characteristic of the red cells is that they are actively phagocytic. Boyd, who regards Ewing's classification as pathologically confusing, prefers to speak of two types of sarcoma, namely a lymphocytic and a reticulo-endothelial type.

Lymphosarcoma invariably terminates fatally, although patients sometimes live from ten to twelve years under appropriate x-ray treatment. Our experience has been that treatment is most effective and remissions longest when the lymphosarcoma is confined to the superficial glands and thorax, and its benefits extremely transient when the process invades the intestines or bony structures.

#### IV ADENOPATHY ORIGINATING PRIMARILY IN THE RETICULO-ENDOTHELIUM OF THE LYMPH GLAND

**Infectious Mononucleosis** —In medical literature, infectious mononucleosis and Pfeiffer's glandular fever are mentioned synonymously, but, as we stated above in connection with Pfeiffer's glandular fever, we do not believe, from the hematological standpoint, that this is justifiable.

To begin with, the monocyte is an entirely different cell from the lymphocyte. It is derived from the endothelial cell and has a phagocytic property which the lymphocyte has not, as demonstrated beyond any doubt by Liebmann<sup>26</sup> in a case of melanomatosis where the monocyte took up the melanin. If the monocyte were to be classed as a lymphocyte the presence of abnormal monocytes in the blood which constitutes monocytic leukemia would likewise cease to be an entity. So long as we accept the abnormal monocyte as an entity as we do in monocytic leukemia it seems to us absolutely rational to accept the abnormal increase of normal monocytes as a disease *sui generis*. Even Longcope,<sup>27</sup> who looks upon both diseases as one, admits that in some cases there is proliferation of the lymphocytes while in others there are atypical monocytes with a proliferation of the endothelial cells, is it not reasonable to suppose that in the first instance the condition is Pfeiffer's glandular fever and, in the second, infectious mononucleosis?

In addition to the variation in the blood pictures of the two conditions, there are very striking clinical differences. That these may be readily appreciated while infectious mononucleosis is under discussion we are prefacing the description of that condition by a brief recapitulation of the clinical and hematological findings in Pfeiffer's glandular fever.

Pfeiffer's glandular fever is generally a disease of childhood most often occurring in epidemic form. The lymph glands enlarge in many regions simultaneously with the appearance of systemic symptoms. Throat symptoms are mild or absent altogether. There is no pain in the long bones and no tendency to hemorrhagic diathesis. Secondary anemia is very



slight The blood invariably shows a marked increase in mature lymphocytes (often to 90 per cent) and a complete absence of eosinophils, with a normal or nearly normal monocyte count (2 to 10 per cent) Recovery is rapid and complete

Infectious mononucleosis, on the other hand, is a non-epidemic disease of adult life, affecting primarily the reticulo-endothelial cells. It sets in with a severe, sometimes ulcerative, always extremely painful sore throat The disease often involves the gums, also, causing bleeding, gingivitis and stomatitis Vincent's spirilli may be recovered from the exudate as secondary invaders

No enlargement of the glands is present until a few days or a week after onset, except possibly the posterior cervical glands, which are the first to be involved By the end of a week, the inframaxillary, axillary and inguinal glands have begun to enlarge and the spleen is invariably enlarged The glands are not painful to touch and their overlapping skin is freely movable

The temperature is elevated, particularly during the active stage of throat symptoms, when it may rise to 105° F There is headache, and pain is present over the entire body, especially in the long bones, caused, evidently, by functional disturbance of the endothelium in the bone marrow

The first impression is sometimes of lymphatic leukemia or myeloblastic leukemia, because of the severe throat symptoms, but a blood examination discloses the nature of the disease The monocytes are greatly increased (20 to 40 per cent) The leukocytes are but moderately elevated and sometimes reduced The polymorphonuclears are normal in size and shape although occasionally an immature white cell is seen The red blood cells, hemoglobin and blood platelets are normal In other words, infectious mononucleosis is a benign hematopoietic disease involving only certain of the blood elements

An important diagnostic test for infectious mononucleosis is the Paul-Bunnell test<sup>15</sup> which is positive if there is a rather high concentration of heterophil antibodies demonstrable in the form of sheep cell agglutinins

The course of infectious mononucleosis is protracted. The throat symptoms abate and the temperature returns to normal within two weeks or so, but the inframaxillary and cervical glands continue to be enlarged for a month or more, and the blood picture persists for a still longer period. In one of our cases, objective recovery was complete within eight weeks, but it was a year before the excessive monocytes disappeared from the blood, and so long as the monocytes were abnormally increased the patient was subjectively uncomfortable in that she tired readily, had a capricious appetite and was irritable. She was pale and had a persistent secondary anemia.

During the acute state, treatment is symptomatic. The throat symptoms, which are most annoying, are relieved by the application of dilute salvarsan to the throat and gums, followed by a gargle of Dobell's solution, 1 tablespoonful in half a glass of water. The temperature, as a rule, is not sufficiently high to require attention but if it should go above  $103^{\circ}$  F, quinine hydrochloride 0.3 three times daily is helpful. Should headache, also, be present this should be given in conjunction with amidopyrine 0.3 but not to exceed 3 or 4 doses. The bowels are to be kept open by mild saline laxatives such as magnesium citrate. It is best to caution the patient not to take calomel because of its aggravating effect on the condition of the mouth. Because of the mouth, the diet has to consist of nonirritating foods, largely of fluids such as iced milk or iced cream, and plenty of water, preferably nonsparkling Vichy.

After the subsidence of the acute symptoms, the diet may be increased rapidly. Owing to the tendency of the anemia to persist, liver cooked in any form should be added to the diet almost daily. Iron in the form of ferri reducti 0.3 and acid arsenosi 0.003 in pill form should be administered three times daily.

Recovery is so extremely slow that some of these patients cannot resume work for weeks or months. To hasten the return to perfect health a change of climate for several weeks may be necessary. It is well to pay attention to after treatment, during convalescence, until the blood returns to normal.

**Monocytic Leukemia** — Monocytic leukemia occurs most often in the adult male. It is characterized by enlargement of all of the superficial glands, particularly those in the groin, neck and axilla. The spleen is invariably involved.

The onset is usually acute, beginning with a sudden elevation of temperature, malaise, pain in the lower extremities, and hemorrhagic diathesis manifested by bleeding from the mucous membranes of the mouth and, very occasionally, by petechiae and ecchymotic spots.

The blood picture is most difficult to interpret. The white cells are only moderately increased, although in a minority of cases they number 30,000 or 40,000. In a case reported by Goldschmidt and Isaac,<sup>28</sup> the blood picture was aleukemic. The polymorphonuclear cells are markedly diminished in number and are largely immature. Myelocytes and myeloblasts are present (1 to 5 per cent). The predominant cells, of course, are the monocytes, 40 to 60 per cent being present in most cases. Hoff<sup>29</sup> has reported a case with 40 per cent monocytes, which were distinctly like endothelial cells in that they possessed a kind of tail. In Hoff's case, the leukocytes did not exceed 2500 at any time. Damashek<sup>30</sup> has reported a case with 65 per cent monocytes, only 12 to 19 per cent of which were of the usual type, and refers to the condition as aleukemic reticulosis. The characteristics of the unusual monocyte, in Damashek's case, were the following: The cell was large, round or polygonal, two or three times normal in size, its cytoplasm was weakly basophilic, and had many coarse granules, the boundaries were irregular with pseudopods, the nucleus of the cell was round, oval or spongy, and there was a negative oxidase reaction. Reschad and Schilling-Torgau,<sup>31</sup> who reported the first case of monocytic leukemia, have shown, also, that most of the monocytes are oxydase negative or, at most, only slightly positive.

The course of monocytic leukemia is acute, rarely subacute, and invariably terminates fatally since it is a malignant disease involving all of the hematopoietic elements. The average duration is from six to ten weeks.

**Hodgkin's Disease**—Of the many names (including pseudoleukemia, anemia lymphatica, generalized lymphadenoma, lymphoblastoma, and aleukemic reticulosis) under which Hodgkin's disease has been described, Hodgkin's lymphogranuloma best fits the clinical and pathologic picture

The disease occurs generally between early adult and middle life, but cases have been encountered in infancy and as late as the eighth decade. It is twice as common in the male as in the female.

*Mode of Distribution of the Affected Glands*—Hodgkin's lymphogranuloma is characterized by enlargement of the glands, generally beginning with those in the neck, either unilaterally or bilaterally. It is to be noted, at the outset, that lymphogranuloma is a widespread disease, occasionally omitting no part of the body where there is lymphoid tissue with endothelium, as in a case described by Ginsberg.<sup>22</sup> Other than the enlargement of the external glands, the patient may have no symptoms whatever.

Cases have been encountered where the parotid gland was the first to enlarge. Should there be co-involvement of the lacrimal gland, the erroneous diagnosis of Mikulicz's disease is not uncommon.

Again, the only noticeably enlarged gland for a year or more may be in the supraclavicular region, giving rise to no subjective symptoms during this period.

Under very rare conditions, a gland in some remote, unsuspected part of the body may be affected and lead to fatal termination before a diagnosis can be reached, as illustrated by a case where the pituitary was completely destroyed, giving rise to the symptom complex of Simmonds' disease.<sup>23</sup> More rarely, the disease is confined to the cerebrospinal system, simulating tumor of the brain or spinal cord. Sometimes a gland near the stomach is the only one to be affected, or the spleen alone may be involved, as exemplified by cases to be described below.

In many instances, the intrathoracic glands are invaded, particularly the glands in the mediastinum, left hilum, and

paratracheal region, and, less often, the intra-abdominal glands are affected. The process may be confined to these regions or exist there in association with involvement elsewhere. Symmers<sup>34</sup> claims, on the basis of postmortem findings, that thoracic and intra-abdominal involvement is much more frequent than the clinician realizes. Of course, if these glands give rise to no symptoms it may be impossible for the clinician to detect their involvement, in many of the cases quoted by Symmers, death was due to some intercurrent disease without a suspicion, during life, of the presence of lymphogranuloma.

As a rule, however, if the thoracic glands are involved, some of the supraclavicular glands are affected, and, in the case of intra-abdominal lymphogranuloma, the inguinal glands are generally enlarged.

The spleen is considerably enlarged in most cases of Hodgkin's, irrespective of the distribution of the lymphogranuloma, but in intra-abdominal Hodgkin's it is invariably enlarged. In fact, this enlargement of the spleen is such a leading sign that in the presence of palpable masses in the abdomen suggesting a diagnosis of intra-abdominal Hodgkin's, such a diagnosis should not be made unless the spleen is enlarged.

*Etiology*—Although the search for the etiologic factor of Hodgkin's lymphogranuloma has been extensive and most diligent, it is still unknown. Therefore, we shall mention only the most plausible. At one time Sternberg,<sup>35</sup> as well as Frank and Much,<sup>36</sup> advanced the theory that it is a modified form of tuberculosis, that is, avian tuberculosis. In support, Steiner<sup>37</sup> showed that individuals afflicted with Hodgkin's lymphogranuloma are more sensitive to avian or human tuberculin in a dilution of 0.001, as shown by a skin reaction, than to a stronger concentration. In other words, Steiner contends, individuals who have had tuberculosis and have acquired an immunity to it, are susceptible to Hodgkin's disease. More recently, Symmers and others have discarded this conception entirely as a result of having proved beyond any doubt that lymphogranuloma can occur in any individual, independent of tuberculosis.

Gordon<sup>38</sup> believes that there is a filtrable virus which is specific for lymphogranuloma and bases his opinion on the following experiment. A suspension obtained from a Hodgkin's gland that had been macerated and had stood for two weeks was injected intravenously into a great number of rabbits, resulting in muscular rigidity, spastic paraplegia, and marked wasting, none of these symptoms followed the injection of the substance of normal, tuberculous or lymphosarcomatous glands. Ogilvie and van Rooyen<sup>39</sup> have confirmed the Gordon experiment and have demonstrated its value as a diagnostic aid.

Owing to the fact that the cervical and inframaxillary glands are so often first to be involved, some authors are of the opinion that the entrance of the invading etiologic factor, presumably a filtrable virus, is by way of the throat, tonsils or pharynx, and that the glandular involvement is secondary. Others again, led by Wessler and Jaches,<sup>40</sup> state that the first gland to be affected is so frequently in the paratracheal region, more often on the left side, that the entrance of the invader must be through the respiratory apparatus. However, lymphogranuloma is a primary adenopathy. So whatever the invading agent may be, there is absolutely no clinical or scientific proof, as yet, of its mode of entrance. It is just as likely that the filtrable virus enters by way of the blood, indeed, this would explain why almost any lymph gland in the body may be the one first to be enlarged.

*Pathology*—It is generally agreed that the disease affects primarily the reticulo-endothelial system, and, preferentially, the reticulo-endothelium of the lymph glands.

Pullinger<sup>41</sup> considers it to be a primary reticulum hyperplasia with secondary involvement of the endothelium. When the reticulum is the more affected, there is greater hematopoietic disturbance and, pathologically, there is a predominance of fibrosis with obliteration of the lymph sinuses and an almost complete obliteration of the corticomedullary portion of the gland. On the other hand, when the endothelium is the more involved there is deformity of the endothelial structures with proliferation of the endothelium, less fibrosis, and less destruc-

tion of the lymphocytic portion. If the reticulum is more affected, there is marked diminution of the lymphocytes in the blood, and an increase in monocytes, whereas, if the endothelium is more involved, the lymphocytic element is not disturbed, the lymphocytes in the blood being normal, or, if increased, this is due to stimulation of the corticomedullary portion. The conception of Pullinger is most helpful, not only from the clinical standpoint but, also, from that of the pathologic study of the gland proper.

The enclosed lymph gland is large, firm, irregular and discrete, it is gray or shell pink, with a moist translucent appearance as of fish flesh. In the late stages, opaque, yellow, suet-like areas of necrosis are present. The capsule may be adherent to the surrounding tissues. Similar masses are found in the spleen, liver and bone marrow.

Microscopically, the most noticeable feature is a proliferation of the reticulo-endothelium of the gland with displacement of the lymphocytes. The new cells are large and pale with vesicular nuclei, so closely resembling the epithelioid cells of tuberculosis that great difficulty is occasionally encountered to differentiate between Hodgkin's lymphosarcoma and hyperplastic tuberculosis. In most cases, the clue is furnished by the presence of mononuclear giant cells with indented nuclei. Eosinophils may be present, brought to the gland, according to Symmers, by the blood stream from the bone marrow. Plasma cells may be present. In other words, the cytological picture has a pleomorphic nature that is typical of the disease. Now and then, however, one gland is pleomorphic whereas the adjacent gland presents the picture of tuberculosis or complete fibrosis. So if the two glands are sent to different pathologists, opinion differs. Again, one part of a gland may be characteristic while another is not, so that a false conclusion is reached by the pathologist if he happens to examine only the atypical portion. Degenerative changes and fibrosis appear in the late stages of the disease. As a rule, the lesion is diffuse in the lymph glands and spleen, but is confined to the Kupffer stellate cells of the liver if there is liver involvement.

*Symptomatology* —The course of the disease may be divided, for the sake of convenience, into three stages. First, the period when only the glands are enlarged, secondly, when systemic symptoms, also, are present, and, finally, the cachectic stage.

In practically all stages, of course, there are some systemic symptoms.

When only the superficial glands are involved, the patient generally complains of ready fatigue, lack of ambition, and poor appetite. The facies is almost that of chloranemia, the adenoids or Waldeyer ring are pronounced, and the most marked feminine status in adenopathy is seen in Hodgkin's lymphogranuloma.

As the disease progresses, itching becomes a prominent symptom, being sometimes so troublesome that the skin is covered by scars and pigmented areas due to scratching. In some instances, itching of the skin is the first noticeable symptom. Not infrequently during the stage of itching, eosinophilia is marked, which suggests that the itching and eosinophilia are alike allergic phenomena.

Hemorrhagic diathesis is rarely present.

The temperature may be elevated, especially in the afternoon or when the patient is exhausted. Some authors regard this elevated temperature as an indication that the disease is infectious in nature, but it is more probably the result of the absorption of broken down glands.

In the terminal stage of the disease, the patient is cachectic and so emaciated as to be practically a skeleton. The temperature becomes septic in type (Pel Ebstein) and the patient is continually bedridden.

During the first stage, were it not for the enlargement of the superficial glands, diagnosis would not be suspected in the great majority of cases. The glands are the size of a hazelnut or walnut, a large prune or an orange. They are discrete semisolid with a sharp edge or rather hard, not tender, and the overlying skin is freely movable. Two or three may mat together but they never suppurate unless overtreated by x-ray.



If the glands in the thorax are involved, their growth is so slow as to cause almost no pressure symptoms until they attain such size as to be demonstrable by roentgen examination. An occasional case is seen, however, where the thoracic glands have enlarged so rapidly and extensively that within a short time they occupy the entire thorax and only the most careful clinical analysis differentiates these cases from thymoma, lymphosarcoma, or malignant substernal thyroid. Goldman and Newman<sup>42</sup> have reported two cases where Hodgkin's lymphogranuloma was mistaken for a thyroid tumor, diagnosis being disclosed only by operation and microscopical study. When there is a substernal malignant thyroid or other malignant intrathoracic disease, in the vast majority of cases the supraclavicular glands are enlarged. The differential diagnosis can be aided by the following method, advocated by Twort<sup>43</sup>. A suspension of the excised gland is injected subcutaneously into a guinea-pig, if, in a few days, there is local inflammatory reaction in which no bacteria can be detected, this is positive for Hodgkin's lymphogranuloma because a suspension of normal glands or glands enlarged by other causes will not produce a similar reaction.

The Gordon and Steiner tests, discussed in connection with pathogenesis, are also valuable diagnostic aids.

As the enlarged glands in the thorax begin to encroach on thoracic organs, corresponding symptoms develop. Pressure on the bronchus causes persistent cough, inspiratory dyspnea and sometimes bloody expectoration, pressure on the trachea, hoarseness and expiratory dyspnea, pressure on the thoracic vessels, dyspnea and marked prominence of the vessels of the neck, pressure on the deeper veins of the chest, bilateral or unilateral effusion, pressure on the thoracic duct, chylous effusion, pressure on the vagus, bradycardia, or on the sympathetic, tachycardia and Horner's syndrome (contraction of the pupil on the affected side and enophthalmos).

Should the enlarged thoracic glands be only those in the region of the aorta, the condition may closely simulate aneurysm of the aorta. The fluoroscopical examination of the chest

should be an aid to differential diagnosis because in aneurysm of the aorta the borders are usually smooth and there is marked expansile pulsation. In Hodgkin's disease, as a rule, there is no pulsation in the tumor mass and the borders are irregular so that by examining the patient from different angles one often succeeds in separating the tumor mass from the aorta. Occasionally, however, the tumor mass may directly compress the aorta and give rise to more pulsation in the mass than in an aneurysm, making differential diagnosis impossible. *Vice versa*, an aneurysm of the aorta may be so calcified as not to give any pulsation. Therefore, in these doubtful cases, a most careful search for glands in the supraclavicular or axillary region should be made and any small gland, even though not clinically suspicious of lymphogranuloma, should be excised for diagnostic purposes.

Although the gastro-intestinal tract is rich in lymphatics and lymph glands, Hodgkin's lymphogranuloma (unlike lymphosarcoma) rarely invades it sufficiently to give rise to clinical symptoms. However, should there be such involvement, the glands increase in size so rapidly that intra abdominal pressure symptoms appear very quickly. As a rule, there is enlargement of the inguinal glands, spleen and liver. When there is intra abdominal Hodgkin's, the course of the disease is much more rapid than when only the external or intra thoracic glands are involved.

Rarely, Hodgkin's lymphogranuloma is confined to one intra abdominal gland. A case of this kind was a young man in the twenties, who was well until eight months before death. His illness began with persistent pyrosis, regurgitation of sour fluid and hunger pain. He resorted to the continuous consumption of bicarbonate of soda for the relief of these symptoms and did not consult a physician for several months. Then he went to Dr. Phillip Shapiro who despite a negative x ray examination rightfully treated the patient for peptic ulcer. During the course of treatment, another x ray examination was made by Dr. A. Peshkin and a niche was discovered on the lesser curvature of the stomach (Fig. 85). The patient devel

oped a severe hemorrhage and was sent to Beth Israel Hospital and was transfused. Alkalosis developed which was fatal despite all efforts to counteract it by intravenous injections of calcium and parathormone. Autopsy revealed a large peptic ulcer on the posterior wall of the stomach near the lesser curvature, in the pars media, and an enlarged intra-abdominal gland in the vicinity of the greater curvature of the stomach.

Dr A. Plaut, who performed the autopsy, was immediately suspicious of the ulcer which, he said, did not present a typical picture of gastric ulcer. At first, he thought it might be luetic, but, after a microscopical study of the inflammatory



Fig 85—Pyloric ulcer secondary to lymphogranuloma of an adjacent gland

changes in the vicinity of the ulcer and of the enlarged intra-abdominal gland, he concluded that the gland was a Hodgkin's gland and that lymphogranuloma of the stomach was directly responsible for the gastric ulcer (Fig 86).

It is problematical whether the ulcer in this patient was the direct result of localized lymphogranuloma of the stomach or was secondary to the Hodgkin's gland in the region of the stomach.

Judging from the character of the symptoms for a number of months, it seems to us more likely that pressure of the gland on the gastric vagus was responsible for the hypersecretion

and hyperacidity, which did not yield to ordinary treatment. It is well known that pressure of a gland on the vagus will cause spasticity of the gastric vessels and bring about ischemia with eventual ulcer formation,<sup>44</sup> which would apply well to the case under discussion. In short, we believe that the lymphogranuloma was confined to the gland and that the ulcer was caused by pressure of the gland on the gastric vagus.

Another very interesting, rare case may be quoted. In this instance, the lymphogranuloma was confined to the spleen.

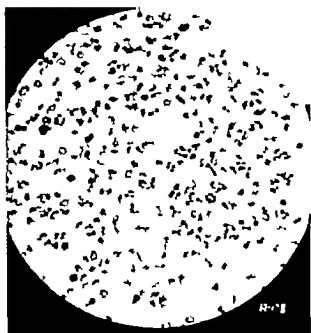


Fig 86.—Microphotograph of section of stomach showing lymphogranulomatous tissue secondary to adjacent lymphogranulomatous gland

The patient, whom we saw through the courtesy of Dr Arthur C Linden, was a woman in the early forties. She became ill with such severe gastric hemorrhage that repeated transfusions were necessary. She responded for a while with slight improvement, but eventually with none at all. Her complexion grew sallow and her blood picture became confusing. The red blood cells and hemoglobin were reduced, macrocytes predominated, and there was leukopenia. The color index was high. The resistance of the red blood cells was increased.

The diagnosis hovered between Addison Biermer's (per

nicious) anemia and hemolytic icterus until, a few weeks before the patient's death, abdominal distention and visible peristalsis of the small intestines suggested lymphogranuloma of the spleen, with involvement of the small intestines. We expressed this opinion but not with sufficient emphasis to prevail against the diagnosis of the hematologist, namely, that the condition was an atypical hemolytic icterus, and so splenectomy was performed.

The spleen proved to be an immensely enlarged, very hard organ. It was unlike the spleen of hemolytic icterus, however, in that it was not filled with blood that could be squeezed out. After a microscopical examination, Doctors A. Plaut and Paul Klemperer agreed that the condition was a peculiar proliferation of the reticulo-endothelial portion of the spleen, but would not commit themselves to say that the spleen was absolutely characteristic of Hodgkin's disease.

Surprisingly, the patient's immediate response to the splenectomy was very favorable. The red blood cells increased in number and the hemoglobin improved. For a few days, it looked as though the removal of the spleen had established the hematologist's diagnosis. Suddenly, however, the patient developed another gastric hemorrhage, which was uncontrollable so that she died.

The microscopical findings in Hodgkin's lymphogranuloma are not always characteristic, and the only outstanding feature in a number of cases is proliferation of the reticulo-endothelium. Moreover, in localized Hodgkin's disease of the spleen there is seldom evidence of the disease elsewhere in the body. So we feel justified in the conviction that this patient's disease was lymphogranuloma of the spleen.

*The Blood Picture*—The blood findings are not characteristic. In a large percentage of cases, there is marked polymorphonuclear leukocytosis, but this is variable, at one stage of the disease there may be 30,000 to 50,000 leukocytes, with 80 to 90 per cent polymorphonuclears, while at other times the leukocytosis and polymorphonucleosis are most moderate. Abnormal white cells are exceptional.

Eosinophils may be present in moderate or high degree. We have encountered cases with 8 to 12 per cent eosinophils, but cases have been reported of between 40 and 68 per cent.

The hemoglobin is more reduced than the red blood cells, which are not generally distorted except for vacuolization corresponding to the reduction in hemoglobin. The blood platelets are not reduced.

The most conspicuous feature of the blood picture is a marked reduction in lymphocytes, though occasionally lymphocytosis is encountered.

When the bone marrow is invaded, the blood picture is still more confusing, in that it simulates subleukemic leukemia or leukemia. In a series of 127 cases reported by Craver and Copeland,<sup>45</sup> 27 had some involvement of the bone, especially of the spine and pelvis, of either the osteoplastic or osteolytic type. Spontaneous fracture was not present, but collapse of the vertebrae was frequent. This extensive bone involvement would undoubtedly be responsible for the severe pain in the lumbar regions and in the long bones experienced by some patients and probably explains the appearance in the blood of many immature white cells, with myelocytes so predominant in some cases as to simulate myelogenous leukemia. When the bone marrow is very extensively involved, the blood platelets may be reduced to a degree to cause hemorrhagic diathesis.

One of our cases was a young adult of twenty five, who came in not long ago because of severe pain in the feet. He complained also of loss of weight, poor appetite and general weakness. Physical examination revealed marked tenderness over the lower extremities, particularly on deep pressure over the calf muscles, and enlargement of the inguinal glands and spleen. The roentgenological examination of the chest revealed enlarged mediastinal glands. The blood picture showed an increase in the white cells with a predominance of polymorphonuclears. The absence of monocytes differentiated the condition from infectious mononucleosis, the case being one of the rare type, known as Ziegler's lymphogranuloma. The patient has greatly improved under x ray treatment.

*Prognosis and Treatment*—The duration of Hodgkin's lymphogranuloma is from six months to fifteen years. Some cases terminate as lymphosarcoma and others as leukemia, but these instances are exceedingly rare. A few cases die of intercurrent tuberculosis.

Remissions are common, with or without treatment.

Rest and nutritious diet are essential. The daily muscular injection of cacodylate of soda in slowly ascending doses from 0.05 to 0.3, then receding, is beneficial in some cases, or, if Fowler's solution is preferred, it should be administered beginning with 1 drop three times a day, increasing by 1 drop a day, until 10 drops are taken three times daily. If the patient does not tolerate arsenic well, as indicated by gastrointestinal symptoms or by pigmentation of the skin, this treatment should be discontinued at once, otherwise it is to be repeated, a rest of one month occurring between courses.

The most successful method of treatment is x-ray therapy, supplemented by medicinal measures. Particularly during the first stage of the disease, x-ray therapy has a most favorable effect in prolonging life.

**Leukosarcoma**—Leukosarcoma derives its name from the fact that the invaded gland has the clinical and often the pathologic characteristics of sarcoma, accompanied by a very marked leukocytosis with a sufficient percentage of immature white cells for the blood picture to simulate leukemia. However, the immature white cells do not reach a percentage high enough to substantiate this suspicion.

The clinical involvement may be localized for a long time, being confined to a gland or group of glands in one location, on the neck, near the parotid gland, or intrathoracically. Rarely, it is diffuse, being marked by leukosarcomatous areas scattered over the skin. Of all the hematopoietic diseases, invasion of the skin with small tumefactions of the nature of the disease, is most common in leukosarcoma. When only one group of glands, including the parotid and lacrimal, is involved, the disease is known under the name of the author who originally described it, that is, Mikulicz disease.





active changes so that the gland enlarges and hardens. This reaction may be confined to the reticulo-endothelium, or it may spread to the corticomedullary portion obliterating the sinuses and replacing the lymphatic structures with connective tissue. Sometimes the capsule of the gland is also affected.

**Silicosis, Anthracosis, Chalicosis**—Adenopathy due to the absorption of foreign substances by the reticulo-endothelium is found most frequently in stone cutters, brick and mine workers. Almost every adult, however, absorbs dust and coal particles so that in everyone some degree of anthracotic glands in the hilum is present, without clinical significance. In the occupational diseases, a greater quantity of foreign substance is taken up by the respiratory tract, especially by the bronchi, leading to changes in the parenchyma of the lungs and bronchi. If there is very marked involvement of the glands, those in the hilum are most often affected, the glands becoming as large as a hazelnut or walnut. They may be so diffusely affected as to simulate tuberculous glands or mediastinal carcinoma. They rarely grow large enough, however, to cause pressure on nerves or vital organs, and are generally accidentally discovered during a routine x-ray examination of the chest.

**Metabolic Disturbances—Gaucher's Disease**—Certain disturbances in metabolism, particularly pertaining to lipoids, give rise to enlargement of the spleen, with or without glandular involvement elsewhere in the body.

Gaucher's disease is prominent in this group. It is usually congenital and familial, seldom hereditary. The lipoid, kersasin, which belongs to the cerebroside, is stored in foam cells of large size known as Gaucher cells. According to Ludwig Pick, these cells are derivatives of the reticulum cell, especially of the spleen, liver, lymph glands, bone marrow, tonsils, and the lymph tissue of the intestines, lungs and cerebral cortex.

The disease is commonest in the Jewish race and is more often encountered in the female than in the male. The onset is insidious, the enlargement of the spleen being so gradual that it gives rise to very few symptoms. By the time the patient consults a physician it may fill almost the entire left side of

the abdomen Irrespective of size, the patient experiences no spontaneous pain and none on palpation

Pigmentation of the exposed skin, due to hemosiderin as a result of the increased blood destruction, is present in 50 per cent of the cases Another important finding is pinguecula, or a yellow, wedge-shaped discoloration of the sclera or conjunctiva, which is characteristic, though not significant if absent Definite hemolysis is demonstrable in some cases, by the diminished resistance of the red blood cells

A typical symptom, and one that should be inquired into if the patient does not volunteer the information, is discomfort in the extremities This is sometimes mistaken, in children, for "growing pains" or, if the pains are severe, for osteomyelitis It is caused by increased subcortical pressure  $\times$  Ray examination will demonstrate definite changes of osteolysis, and an irregularity of the cortex, in most cases

If the liver is involved, the patient develops hyperchrome anemia with leukopenia and a reduction in blood platelets With this reduction in blood platelets, hemorrhagic diathesis appears Occasionally, instead of leukopenia, there is lymphocytosis, as in three cases described by Enzer<sup>46</sup> and in one case reported by Anderson<sup>47</sup> Anderson's case was most interesting because it was actually hereditary The lipophages stain blue with Mallory's tricolored stain

Splenectomy is generally advised as the treatment of choice However, removal of the spleen cannot be regarded as a curative measure for the reason that this disease also affects the reticulum in every part of the body Indeed, one must be very cautious in recommending splenectomy because should there be bone involvement such a procedure will aggravate the condition A very careful examination of all bones must be made, therefore, before the radical advice of splenectomy is given and then it should be carried out only if local symptoms in the abdomen and hyperchrome anemia, with symptoms of hemorrhagic diathesis, are present

If splenectomy is contraindicated,  $\times$  ray therapy should be carried out Should anemia be a prominent symptom, pallia

tive treatment should be the following Large doses (10) of iron and ammonium citrate three to five times daily for a period of six weeks, followed by six weeks in which the iron is supplanted by 0.05 cacodylate of soda intramuscularly once daily, after which treatment is discontinued for a month

If here is leukopenia, liver should be given by mouth as a food In severe cases with hemorrhagic diathesis, the patient should receive intramuscular injections of liver, 3 cc once every three days and, in addition, one-half pound of calves liver daily or two ampules three times a day

**Niemann-Pick's Disease**—In 1914, Niemann reported a case with an unusual clinical picture The patient was an infant girl, seventeen months of age, with a pale brown, almost waxy though not icteric coloring, an immensely distended abdomen due to a massive spleen and liver, slight ascites, and edema of the eyelids and feet The blood picture was normal Autopsy showed an enormously enlarged liver and spleen, as well as other enlarged intra-abdominal lymph glands The glands were soft and had a peculiar yellow color The kidneys and cortex, also, were strikingly yellow Microscopically this color was found to be due to large, irregularly outlined cells with small, round nuclei and many vacuoles The body of the cell stained a dark, dirty red with Sudan III, indicating a lipid content Niemann concluded that the disease was closely related to Gaucher's disease Later, Ludwig Pick had an opportunity to study several cases most thoroughly and as a result of his confirmation of the findings of Niemann, the disease became known as Niemann-Pick's disease

It is rarer than Gaucher's disease, occurs only in children, and predominantly in Jewish children, especially in the female It is congenital and familial and is essentially an internal xanthomatosis, affecting practically every organ that has an endothelium but with its greatest predilection for the spleen, liver and lymph glands

The superficial glands are usually enlarged The internal lymph glands attain a much greater size, especially those around the liver and the head of the pancreas, the spleen and

mesenteric glands The thymus is almost invariably increased in size The brain may be involved so that idiocy develops, some authors consider that there is a close relationship between Niemann Pick's disease and Tay Sachs' disease (amaurotic idiocy)

The affection is invariably accompanied by leukocytosis, in contradistinction to the leukopenia of Gaucher's disease Because of the lipemia, the blood serum is cloudy The cholesterol content of the blood is elevated, sometimes to as much as 650 mg in 100 cc., but a normal cholesterol content does not exclude the diagnosis

Microscopically, diagnosis is established by the demonstration of characteristic foam cells filled with a lipoid which, during life, is obtained only by puncturing the bone marrow or spleen, preferably the latter The Niemann Pick cell, unlike the homogeneous Gaucher cell, is filled with small, round droplets in mulberry like crustations

Pathologically, the glands including the thymus, as well as the lymph follicles of the intestinal mucosa are yellow due to the presence of the large, pale yellow Niemann Pick cells The lipophages stain a dirty, grayish blue with Mallory's tri-colored stain The chemical reactions of the products of metabolism that are deposited in the large Niemann Pick cells are phosphatids, the basic lipoid of the disease

The general framework of the lymph node remains intact, but the lymphoid tissue is replaced by foam cells to a large extent Phosphatid deposits in the suprarenals affect the cortex but not the medulla, invariably causing enlargement of the suprarenals A similar process may be found in the pituitary and ovary

It is evident from Pick's<sup>45</sup> pathologic description that not only are the glands involved in the storage of lipoids but practically all the tissue elements as well An explanation for this is offered by Pick in the fact that in infancy the macrophage system is widespread with lipoid storage occurring in many additional places after the natural storage locations are loaded

Splenectomy may afford temporary relief and x-ray therapy may prolong life, but the disease is a progressive one, generally terminating fatally in childhood

**Xanthoma Diabeticorum**—Xanthoma diabeticorum is occasionally accompanied by enlargement of the external, often of the internal lymph glands. It is well known that diabetic coma is sometimes preceded by violent abdominal cramps simulating an acute surgical condition in the abdomen. Many theories have been advanced, one of the most plausible being that of pancreatic neuralgia. There is no doubt, however, that acutely enlarged intra-abdominal lymph glands may be the cause of these violent pains in some cases of diabetes mellitus.

If the mediastinal glands enlarge, they may suppurate and give rise to suppurative mediastinitis with fatal termination. In rare cases the glands in the mediastinum or those adjoining the pleura suppurate and cause gangrene of the lung and empyema.

**Carcinomatous Adenopathy**—Primary carcinoma of the lymph glands is almost unknown. Therefore, when there are carcinomatous glands they are to be considered secondary to carcinoma of some organ. The cancer cells are detected first in the sinuses of the gland, though they very quickly invade every portion of it with a tendency to break through the capsule and adhere to adjacent tissues.

Carcinomatous intra-abdominal lymph glands secondary to carcinoma of the colon or stomach tend to suppurate, but the glands in the thorax rarely suppurate unless there is a perforation of the esophagus with invasion of the adjacent glands, in which event suppurative mediastinitis develops.

Occasionally, there is such widespread invasion of the glands that the inguinal, axillary and even the cervical glands are included, simulating lymphosarcoma. The primary lesion may be so concealed as not to be accessible to clinical diagnosis. Only on the postmortem table may a small cancer be found on the posterior wall of the stomach, in a bronchus, prostate, thyroid or suprarenal gland.

In carcinoma of the stomach, a supraclavicular gland on the left side near the inner border of the sternocleidomastoid

(Virchow gland) may be the only one to be carcinomatous. If there is an anomalous thoracic duct on the right side, the Virchow gland may be found on that side.

Palpation of the superficial glands, in most cases, reveals the diagnosis. They are irregular and hard, not tender, and the overlying skin is not reddened and is only partially adherent. It is very important to remember that in many cases, particularly in carcinoma of the colon or adnexa, the glands in the culdesac are enlarged and easily detectable by digital rectal examination.

If one encounters enlarged cervical glands that biopsy proves to be carcinomatous, and no lesion can be demonstrated in any organ, one should search carefully for a primary carcinoma in one of the tonsils because carcinoma may long exist there before giving rise to symptoms.

From the practical standpoint, it is essential to remember that when there is carcinoma of an organ, particularly of the stomach or colon, the surgeon may find enlarged adjacent glands and so be dissuaded from a radical operation. As this enlargement may be purely inflammatory in nature, it is advisable for the surgeon to excise the most suspicious gland for immediate pathologic examination. If no cancer cells are found, the radical operation should be continued to give the patient the benefit of the doubt.

#### VI. ADENOPATHY SECONDARY TO PRIMARY HEMATOPOIETIC DISEASE

**Myelogenous Leukemia**—Whereas in acute myeloblastic leukemia, there may be only moderate enlargement of the cervical glands, accompanying an ulcerative condition of the mouth, in myelogenous leukemia, although primarily a disease of the bone marrow, coaffection of many of the external glands is not an uncommon feature. The lymph organ most affected is the spleen. In fact, the largest spleen next to that in Gaucher's disease or that associated with thrombophlebitis of the splenic vein, is encountered in this disease. Most of the superficial glands are enlarged, particularly the inguinal and

axillary glands, less frequently the cervical glands. The thoracic and intra-abdominal glands, however, are almost never enlarged.

The disease was formerly called "mixed leukemia," meaning myeloid leukemia and lymphatic leukemia. This was a misnomer, however, because the excised gland does not show evidence of a production of immature lymphocytes as in lymphatic leukemia. In reality, there may be evidence of myeloid cell proliferation or myeloid cells brought to the gland through the circulation.

This differentiation in names is not purely academic because the *glandular enlargement in lymphatic leukemia yields very rapidly to x-ray and radium treatment, whereas that accompanying myelogenous leukemia reacts much more slowly to treatment*.

The blood picture is characterized by a marked increase in white cells, which are predominantly myelocytes. Occasionally a few myeloblasts are seen. There is a reduction in hemoglobin and in the number of red blood cells which are often deformed. The hemoglobin is not reduced in proportion to the reduction in red blood cells. The platelets are reduced in number, sometimes to such a degree as to be responsible for hemorrhagic diathesis. The blood picture very often changes in the course of the disease so that the leukocytosis gives way to a normal number of white cells, although abnormal white cells (myelocytes) continue to predominate. Very rarely, there is subleukemia.

Remissions are not uncommon but are usually of very brief duration. Many of these patients die of an intercurrent disease. If they do not, the disease progresses gradually to a fatal termination within one to five years. Appropriate x-ray treatment prolongs life, the patient being perfectly comfortable during remissions, but careful examination of the blood will show but a moderate decrease of abnormal white cells (myelocytes) and always some anemia. Cases have been reported lasting as long as ten years.

Occasionally, extremely active x-ray treatment over the

spleen causes a rather quick diminution in size, but this is fraught with danger. In one case given overactive x ray treatment before admission to Beth Israel Hospital such changes were produced in the spleen that it ruptured causing general peritonitis and death within twenty four hours, confirmed by autopsy.

### STATUS LYMPHATICUS

Although the first appreciation of the clinical significance of status lymphaticus is generally attributed to von Neusser, credit should really be given to Norris for first having recognized it as a pathologic entity.

In 1905, Norris noticed that death due to trivial causes, such as a minor operation or unexplained drowning usually occurs in individuals of a peculiar status. These persons are very frail, the skin light, and, in the young, there is predominance of lymph follicles, nodes and glands, both externally and internally. Microscopically, these lymph glands and nodes show a predominance of mature and large lymphocytes, and a paucity of reticulum.

Norris presented these findings in an address before the New York Academy of Medicine and wrote a personal letter to von Neusser in which he called attention to status lymphaticus as a pathologic entity and requested him to study it clinically. Von Neusser's answer was a brilliant article<sup>40</sup> on "status thymicolymphaticus," in which he stated that the clinical diagnosis of this condition must be substantiated by postmortem findings of a failure of involution of the lymph nodes and lymph follicles in those parts of the body where complete involution is rightfully to be expected.

For a long time, the terms "status lymphaticus" and "status thymicolymphaticus" were used interchangeably. They are not synonymous, however, inasmuch as in every case of status lymphaticus there need not be a persistent thymus, and the persistence of the thymus beyond the normal age with an increase in its size does not, from the pathologic standpoint necessarily indicate status lymphaticus. Hammar,<sup>50</sup> Greenwood and Woods,<sup>51</sup> Young and Turnbull,<sup>2</sup> and other authors,



have shown that in many cases a thymus is larger than normal and present at a time when it should have involuted, yet the most thorough search will reveal no deviation from normal in any of the other lymphatic structures

In 1918, Symmers<sup>53</sup> contributed further valuable pathologic data to the subject of status lymphaticus, and, in 1928, Marine<sup>54</sup> defined it as follows "Status lymphaticus is a constitutional defect, usually congenital though it may be acquired, dependent upon the inadequacy of the suprarenals, sex glands, and autonomic nervous system and associated with lowered resistance or increased susceptibility to a great variety of non-specific physical and chemical agents Anatomically, it is characterized by delayed involution or hyperplasia of the thymus Hypertrophy of the lymph glands and lymphoid tissue of the various organs, underdevelopment of the chromaffin gonads (suprarenal cortex, interstitial cells of the testes and ovaries), and the cardiovascular system, and certain peculiarities of external configuration "

This definition fully corresponds to pathologic findings and is most acceptable from a clinical standpoint The only modification that we would suggest is that it seems to us essential to remember that the "congenital type" of status lymphaticus is, to a large extent, actually acquired The lymphatic nodes, glands and tissues, as stated above, are nature's first line of defense in case of infection, even during intra-uterine life Hence, when there is an intra-uterine infection, the entire lymphatic system responds in defense of the fetus and the child is born with a rich lymphatic system including enlarged lymph nodes and glands In substantiation of this conception may be offered the fact that congenital lues, which is due to an intra-uterine infection, is most often encountered in individuals of lymphatic status

The weakness of the infant who has undergone any intra-uterine infection is responsible for further infection after birth, both of the respiratory and gastro-intestinal tracts, as well as of the glands of internal secretion, with a corresponding influence on growth and habitus The child generally develops

into a very tall, thin individual with a silky, sensitive skin, sparse hair femininely distributed in the male, sunken abdomen, small heart, narrow aorta, obtuse epigastric angle, and, occasionally, a floating tenth rib, in other words, into a status asthenicus which, in the presence of enlarged glands, constitutes status lymphaticus

The approach of puberty is marked by nervous irritability and fatigability, as well as by evidence of neurocirculatory asthenia due to the narrow aorta and small, drop heart in many of these people. The thymus, instead of undergoing involution, may persist and actually increase in size. The tonsils and adenoids are enlarged and subject to repeated infection. Death may occur suddenly as the result of unexpectedly shocking news, either good or bad, during a minor infection, during a minor operation, or while a vein is being punctured to obtain blood for examination. We recall one case, a tall young man of seventeen years, who, in the course of pneumonia, developed empyema. As he was being prepared for the operation, and before the anesthetic was given, the surgeon punctured the pleura in order to verify the diagnosis. As the needle went in, the patient went out.

In most of these cases, microscopical study of the remains of the thymus and other glandular structures furnishes the only clue to diagnosis. In the opinion of Symmers, death is due to anaphylactic shock. This shock and its preceding allergic manifestations are the result of the absorption of necrotic tissue from the glands. This conception is upheld by Waldbott,<sup>53</sup> whose postmortem studies have revealed markedly dilated capillaries in the lungs, liver and other organs of persons whose death has come about through some trivial cause, just as in animals whose death is due to experimental anaphylactic shock. In some instances, Waldbott found petechial hemorrhages in the heart, pleura and lymph glands, in others, there was dilatation of the entire right side of the heart.

From the foregoing, it may appear that a very clear-cut pathologic and clinical picture characterizes status lymphaticus

This is true in a majority of cases. However, it is not always so.

Many individuals of typical status asthenicus are not doomed to sudden death by minor causes, even when they have a narrow aorta and a drop heart. Such persons may, by proper physical and mental regime, reinstate themselves to effective capacity, sometimes actually to the point of going through both physical and psychical trauma with immunity, as so well demonstrated during that great mass experiment, the World War. In our anxiety to prevent unnecessary risk, therefore, it is erroneous to consider all these individuals as liable to a sudden exitus from some trivial cause, for, by so doing, we may inadvertently include many persons not in danger, whose morale should not be lowered, and even interfere with a necessary operation without which the patient may lose his life. It is equally important, on the other hand, to be protectively cautious for the person who has none of the external manifestations of a status lymphaticus but who, nevertheless, actually belongs to this group.

Von Neusser, with his superkeen clinical insight, has furnished the clue by which to make a clinical distinction of status lymphaticus. To determine whether or not a person is really of this status, one must study the manner in which his vital organs respond functionally to the ordinary and, especially, to the extraordinary demands of life.

To illustrate, if an individual during puberty and early adult life responds to disease with lymphocytosis instead of polymorphonucleosis, that person undoubtedly belongs to the status lymphaticus group, this is indicated in the overproduction of mature lymphocytes by his lymph glandular apparatus.

Again, those who develop glandular fever, generally children, and infectious mononucleosis, usually adults, belong largely to this group. That is, the lymph glands are hyperactive, so that the individual has a true lymphatic status not in the fact that his glands are enlarged but because their hematopoietic function is abnormal.

Some individuals in the status lymphaticus group develop

neutropenia or a complete disappearance of the neutrophils from the blood, with symptoms of ulcerative stomatitis or ulcerative areas in other mucous membranes as a result of the administration of certain drugs, particularly the arsenical preparations, noninjurious to persons of normal status. As a rule, the external appearance presents some of the manifestations of status lymphaticus, but not always. It is, therefore, important, when intending to administer arsphenamine, dinitrophenol, or amidopyrine, first to study the blood of the patient to see that there is no lymphocytosis. It is quite likely that even normal children who do not tolerate arsenical preparations and amidopyrine are still in a state of hyperactivity of the lymph glandular apparatus.

We have seen two cases of arsphenamine neutropenia. Both patients were adult males of the status lymphaticus type—tall, thin and frail, with a feminine distribution of hair. Following treatment by transfusion and liver extract, both recovered.

A third case, encountered while this paper was in preparation, was a young girl of thirteen, who, as a result of dinitrophenol poisoning, developed stomatitis and ulceration of the pharynx, with hyperpyrexia, accompanied by the following blood picture: Red blood cells 4,600,000, 84 per cent hemoglobin, 180,000 platelets, 100 per cent small, mature lymphocytes, and a complete absence of neutrophils. This young girl, who weighed 230 pounds, was a typical status thymicolymphaticus.

It has been our experience that agranulocytic angina, including 'dysplastic granulocytopenia' (Weiss and Gold bloom<sup>80</sup>) has a predilection for individuals of status lymphaticus.

When the thymus is responsible for the death of an individual in the course of a mild infection, or while bathing, it is not that gland *per se* that causes death by pressing on the mediastinum to produce asphyxiation, but its failure to cease functioning as a producer of lymphocytes. This is demonstrated by the fact that when the thymus in these cases is

examined postmortem, it is invariably found to be very rich in lymphocytes

In some individuals, status lymphaticus may reveal itself by the presence of an extremely slow heart rate, little influenced by exercise although accelerated by atropin. This slow heart beat is due to a persistent stimulation of the vagus, attributed to thymus activity by many authors who routinely class younger individuals with a slow pulse in the status lymphaticus group. Unexplained death due to drowning is also looked upon as due to a sudden cessation of heart beat on account of overstimulation of the vagus.

In addition to its direct effects, a large thymus may have an indirect effect, for instance, a persistently hyperactive thymus may be a factor in the development of thyrotoxicosis. This is of the utmost clinical importance because such an individual responds poorly to thyroidectomy unless the thymus, also, is operated upon. Von Neusser has attributed the moderately slow instead of the increased pulse in some cases of thyrotoxicosis to the vagus effect of the thymus on the heart. An enlarged thymus, with or without thyrotoxicosis is, of course, usually diagnosticable by means of the x-ray. It is to be remembered, however, that during the first years of life the thymus is demonstrable in most cases without symptoms, so that roentgenological evidence alone is not sufficient for a diagnosis of status thymicolymphaticus.

When the lymphatic status tends to influence the glands of internal secretion, there are usually warning manifestations. If the adrenal cortex is unduly influenced the patient has an extremely low systolic pressure (always below 100) and is subject to fainting spells. He suffers, also, from actual hypoglycemia, with a craving for sweets that viciously cannot be tolerated. A minor operation, or the slightest infection, in such an individual almost inevitably produces fatal hypoadrenalemia. In other persons, the suprarenal glands may be so sensitive that any mild infection causes a bacterial invasion of these glands, followed by necrosis, as shown at autopsy. Most cases of Addison's disease, also, are individuals of this status.

Another pathologic condition of status lymphaticus that occasionally causes sudden death is hyperplasia of the vagus nucleus in the medulla oblongata, manifesting itself during life by instability of cardiac action. Such individuals have a persistently slow pulse, sometimes only 40 beats a minute, almost unaffected by exercise. There is marked respiratory irregularity, particularly during sleep, in fact, death is apt to occur when the individual is asleep, particularly during childhood or puberty. In other persons, death occurs during a cold bath or upon the receipt of sudden news, being directly attributable to an abnormal vagus response on the part of the circulatory or respiratory apparatus.

Occasionally, in addition to the narrow aorta there are narrow coronary vessels which, even during early adult life, insufficiently nourish the heart when it is under moderate physical strain so that the patient suffers from precordial pain, pain in the left arm, and tachycardia on the least exertion, succumbing at an early age—perhaps in the twenties—to coronary thrombosis. Postmortem examination of the soldier, the runner, or the lightweight prize fighter who has died suddenly will often reveal not only a narrow aorta and narrow coronary vessels, but, also, enlarged paratracheal lymph glands and an incompletely involuted thymus. In other words, the combination of status lymphaticus and hypoplastic blood vessels is the cause of death, not merely hypoplasia of the blood vessels. In some cases, reported by von Neusser, lymphatic infiltration of the bundle of His is present. Von Neusser called attention, too—remarkably, long before the era of the Wassermann reaction—to the fact that luetic aortitis is most frequent in individuals of the status lymphaticus group having a hypoplastic aorta, a clinical observation later confirmed by Symmers in a study of pathologic material.

#### SUMMARY

1. An attempt has been made to classify the adenopathies according to structural changes in the gland and the functional disturbances caused by such structural changes.

2 The two most important portions of the gland, that is, the corticomedullary with its lymphocytic elements and the reticulo-endothelium with its multiplicity of functions, were discussed and the diseases common to the lymph glands were described from the angle of disturbed function in each of these parts

3 In most adenopathies, particularly toward the end, in whatever part the affection may have started, there is usually invasion of the other portions of the gland. Not infrequently the hematopoietic system, which is an integral part of the lymph gland, is involved. Hence, from the standpoint of pathologic study, which is usually of the end-result, this classification may seem artificial. However, it is felt that the study of the effect of a disease of an organ must be appreciated from its inception and this can be done only if the disturbed function of the original part is understood.

4 That very difficult chapter in medicine, namely, status lymphaticus, has been discussed not only from the standpoint of external appearance but, also, from that of disturbed function. An effort has been made to show that status lymphaticus is not always congenital but rather, in the vast majority of cases, acquired through some intra-uterine infection that has given rise to enlargement of the glands at that time and later to poor physical development. In the determination of whether or not an individual is in the status lymphaticus group, the distribution of the lymph glands and their effect upon circulatory, respiratory, internal secretion and hematopoietic function is more important than external appearance.

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In order to plan intelligent treatment of any enlarged lymph node or group of lymph nodes it is essential that the nature of the lymphadenopathy be discovered as nearly certainly as possible. In some cases physical examination alone may show the reason for the presence of the swollen nodes. In some cases, on the other hand the nature of the process remains obscure even after careful microscopical examination of tissue removed by biopsy. In the ensuing discussion of treatment of the more important types of lymphadenopathy, the outstanding clinical features of each are briefly reviewed in order to give a clearer conception of the basis for the modes of treatment suggested.

The varieties of lymphadenopathy here considered may be divided roughly into malignant, or those which either frequently or invariably signify the presence of a fatal disease, and the benign, which are of inflammatory or metabolic origin, and represent in general the existence of diseases affecting more

chances of recovery In the malignant group are carcinoma, lymphosarcoma, leukemia, Hodgkin's disease and mycosis fungoides

In the benign group we consider only tuberculous lymphadenopathy and infectious mononucleosis Syphilitic lymphadenopathy is seldom of importance *per se*, and need not be discussed here The other inflammatory and metabolic lymphadenopathies are chiefly of interest from the diagnostic viewpoint, the treatment usually being obvious and not separable from the treatment of the disease as a whole, once the diagnosis is made

Of the malignant lymphadenopathies, Hodgkin's disease, lymphosarcoma, leukemia, and mycosis fungoides may be regarded at present as practically inevitably fatal Therefore, the treatment should be planned with the purpose in mind of securing the best possible palliation It is important to recognize those cases which tend naturally to run a longer course than the average, and in such instances to refrain from doing something that may shorten the course Individualization, close observation and accuracy in treatment are requisites to successful palliation

In all of this particular group of lymphadenopathies external irradiation by x-rays or radium is the main resource This has been carried out in the past mainly by exposing separate local areas of the body to the source of radiation Another mode of irradiation has attracted interest in recent years, namely, irradiation of the entire body (teleroentgenotherapy, spray treatments, Heublein method)<sup>1 2 3</sup> This method has furnished very encouraging results in these radio-sensitive processes, and will probably come into more general use

Various adjuvants are of considerable importance in this group Arsenic, iron, sunlight, transfusions, may be of great aid Rest, alone, may be the treatment of choice, at times, for many cases in this group, and is always one of our best allies in combating the symptoms Various experimental methods, such as the use of gland filtrates and avian tuberculin in the

treatment of Hodgkin's disease, are regarded as without the scope of this discussion

### TUBERCULOUS LYMPHADENITIS

While a generalized form of tuberculous disease of the lymphatic system is known, it is comparatively rare. With few exceptions tuberculosis of the lymph nodes produces enlargement in only one group or a few associated groups of nodes, one group nearly always predominating. There is seldom any evidence of tuberculosis elsewhere. The textbook description of nodes that are matted together, of softening from caseation and of sinus formation can by no means be applied to the majority of cases, if early diagnoses are to be made. In fact, the early diagnosis of tuberculous lymphadenopathy in differentiation from other adenopathies, banal or malignant must rest almost solely on biopsy. The differentiation from Hodgkin's disease is particularly difficult, at times even with the aid of adequate biopsy material. The more experienced the pathologist, the more cases are seen in which decision is reserved in differentiating between tuberculosis and Hodgkin's disease of an excised lymph node.

Once the diagnosis of tuberculosis is established the choice of treatment lies between three methods

- 1 Surgical removal
- 2 A prolonged course of natural or artificial heliotherapy
- 3 Irradiation with  $x$  rays

In suitable cases and in the hands of experienced operators surgical extirpation offers excellent results, and must be particularly considered when it is necessary that the patient be speedily rid of his disease and returned to economic usefulness. However, such operations are usually disfiguring and seem unfortunate in cases occurring in children and young women. It is not uncommon, moreover, for surgical removal of tuberculous nodes of the neck to result in impairment of the spinal accessory nerve.

The ideal method of treatment of tuberculous nodes would seem to be the same as has been shown to be so beneficial for bone and joint tuberculosis *i. e.*, prolonged sanatorium care

including methodical exposure of the whole body to sunlight and the quartz lamp. Much can be done for many patients along similar lines at their homes. One important point to keep in mind is that if tuberculous nodes are exposed to excessive amounts of sunlight in the beginning, they may break down. It is probably best to shield the diseased area at first, allowing sunlight to reach only the other parts of the body and to increase the dose of sunlight to the diseased area gradually.

Either by itself, or, preferably, in combination with rest and general heliotherapy, may be pursued the method of treatment by  $x$ -rays. This method requires patience and a confidence in reassuring the patient in the face of apparent lack of results in the early weeks of treatment. The doses of  $x$ -rays should be small, not over 100 r of high or low voltage at a time. It has seemed to the writer that it is best to await the results of one dose for at least two to four weeks before repeating. In this way there is less chance of causing too massive a breaking down of the nodes. When a single node softens and becomes fluctuant, it may be possible to avoid the formation of a large sinus by repeated aspiration of the broken down material, thus relieving tension on the skin. If this is done, the needle should be introduced from the side, so as to spare that part of the skin lying directly over the node. Usually a small sinus will form at one of the sites of puncture, but as a rule will heal within a few weeks.

Larger doses of  $x$ -rays, such as 300 to 400 r, even if only with low voltage (130 to 140 kv) are quite likely to cause massive breaking down, with consequent discomfort, formation of large sinuses, delayed healing, and possible danger to the patient's health. In this event it would seem that the danger of rupture into a vein and miliary dissemination would be greater than in cases not thus complicated.

#### CHRONIC LYMPHATIC LEUKEMIA

The term "leukemia" covers a wide range of disease processes. At one extreme they approach closely to, and probably merge with, various infectious and reactive states. At the other

extreme they assume the form of highly malignant true neoplasms. Borderline and transitional cases are found, linking leukemia to lymphosarcoma, Hodgkin's disease, Mikulicz's disease, mycosis fungoides, pernicious anemia, and polycythemia vera. The scope of the so-called "monocytic leukemia" is still to be defined. The present discussion of the treatment of leukemia will be confined to the more typical lymphatic and myeloid forms.

The most pronounced examples of general lymphadenopathy are seen in chronic lymphatic leukemia which, in its typical form, is characterized by a remarkably symmetrical distribution of enlarged lymph nodes, tending to remain discrete, though closely packed together in groups. There is also a strong tendency to develop adenopathy in unusual sites, such as toward the lateral side of the breast, the suprascapular, epitrochlear, anterior femoral, and popliteal regions and along the inner side of the upper arm. There is frequently found a large central abdominal mass, consisting of greatly enlarged retroperitoneal and mesenteric nodes, or a less definitely outlined general abdominal fulness, sometimes with palpable rounded masses scattered about. Often both the liver and spleen are considerably enlarged, and frequently there is some enlargement of the mediastinal or hilar nodes. Exceptional cases are seen, designated by the French as the splenic type of lymphatic leukemia, in which the spleen is greatly enlarged and in which there may be at first little or no external adenopathy. Such cases thus simulate, at first glance, the myeloid form of leukemia. In young patients, particularly, there may be a huge mediastinal tumor, probably caused in most instances by lymphoid tumefaction of the thymus.

Practically all of the above mentioned physical findings may be presented by cases in which the blood count furnishes no clear evidence of leukemia. Such cases are classified clinically as lymphatic pseudoleukemia. Other cases present a similar clinical picture, together with a low grade type of leukemic blood count, or subleukemia. No doubt the fundamental pathologic disturbance is the same in all these cases, the blood

picture being more or less incidental. Gross lesions of bones are apparently more common in this type of leukemia than in the myeloid form, although still relatively uncommon, as compared with Hodgkin's disease and lymphosarcoma. The gastrointestinal, urinary and other systems may be invaded.

Because of the wide distribution of gross lesions that cause symptoms in this disease, and the numerous variations, it is difficult to discuss treatment in general terms. We may take as an example a typical case of chronic lymphatic leukemia in a middle aged or elderly patient, presenting the usual generalized external and internal lymphadenopathy, with moderate enlargement of the spleen and liver, and a blood count showing slight anemia, 300,000 white cells, and 90 per cent small lymphocytes. In such a case, the procedure is customarily to irradiate the external masses of lymph nodes, one group at a time, at intervals of from one to three days, with about 300 r of high voltage x-rays (Factors 200 kv peak, 4 to 30 ma, 50 cm distance, 0.5 mm Cu). This serves as a test, both of the sensitivity of the nodes in this particular case, and the response of the blood count. Relatively seldom does one observe a marked or complete regression of the nodes from such a course of treatment, but one may find that the blood count within a month or so has been reduced to 50,000 white cells or less, with or without a corresponding decrease in the percentage of lymphocytes and a concomitant increase in the percentage of polynuclear cells.

Depending on the degree of this response, a decision is then made as to the wisdom of proceeding to give similar treatment to the deep lymph nodes, those in the mediastinal and retroperitoneal regions. Thus, if the white cell count has fallen to 10,000, and the polynuclear cells have increased in percentage to 50 or 60 per cent, and the patient's general condition has improved, and some regression of the treated nodes has occurred, it seems best to be satisfied temporarily and to await either some new evidence of activity of the disease, or the passage of two or three months more, before subjecting the patient to more radiation. If, on the other hand, the patient has not

withstood this small amount of treatment well, showing undue loss of strength, and perhaps the appearance of a hemorrhagic tendency or an increase of a preexisting slight hemorrhagic tendency, if the nodes have not regressed appreciably, and the white count has failed to fall, or has fallen too far, or the differential count shows no improvement or has grown worse (100 per cent small lymphocytes, or a large percentage of fragile cells), one would hesitate to give further radiation at that time (With so many variables to consider, the above criteria cannot be accepted as always binding, and it must be emphasized that decisions made in treating these cases are at present largely empirical, based on experience. No single factor or set of factors can be selected as a routine guide. Any attempt to determine treatment by some single measure, such as the blood count, or the basal metabolic rate, will surely lead to more errors than are made when the whole picture of the case is assembled and allowed to form the basis of a sort of intuitive judgment as to what is needed.)

If the white count has dropped to only about 50,000 and there has been only a moderate shift toward normal in the differential count, and the patient's general condition has not been much disturbed by the first cycle of x ray treatment, one would feel safe in proceeding to irradiate the deep nodes with similar doses. For this purpose a central zone about 10 cm wide on the surface is mapped out along the length of the trunk anteriorly and posteriorly, and usually divided into upper, middle and lower thirds. Thus three rectangular fields cover the mediastinal and retroperitoneal nodes anteriorly, and three fields posteriorly. To each may be given 200 to 400 r of high voltage x rays usually in a single exposure per field, at intervals of from one to three or four days. Unless the spleen and liver are greatly enlarged, they are often neglected at least in these earlier cycles of treatment.

Subsequent treatment consists either of a repetition of the foregoing cycles, as the indications arise judged by the condition of the patient and the passage of time, or of irradiation of particular areas where symptoms or demonstrable disease



may be discovered in the course of the routine follow-up examination. These patients should be seen regularly at intervals of from two to six weeks, the intervals depending on the individual case.

The leukemic patient is prone to develop infection. A cellulitis or an abscess may run a very obstinate course. Rapid improvement and complete healing can often be brought about by treating the infected area with low voltage, lightly filtered x-rays, in small doses, such as 100 to 200 r.

One of the minor features of chronic lymphatic leukemia is the fairly frequent occurrence of leukemic infiltration about the orbit, particularly about the lacrimal sac. This condition is occasionally mistaken for dacryocystitis, the existence of leukemia being discovered when a search is made for the cause of the failure of the operative wound to heal properly. These infiltrations can often be abolished completely by small doses of x-rays, with no appreciable damage to the eyes.

**Results in Lymphatic Leukemia**—The effects of irradiation for chronic lymphatic leukemia are, in general, less spectacular and immediately satisfying than for myeloid leukemia. Some cases respond very well, others seem to be completely nonresponsive. There is no way of telling what the response will be, and therefore practically all cases are treated. The disease is so variable in duration that figures as to average length of life following treatment probably are of little real value, less than for myeloid leukemia. However, Arendt and Gloor<sup>4</sup> thought they obtained better average results by local irradiation of lymphatic leukemia than in myeloid leukemia. In using the Heublein method of prolonged continuous irradiation of the entire body we thought some cases did better, showing a smoother and more prompt regression, than with local irradiation. We also thought that lymphatic leukemia responded better to general irradiation than the myeloid form<sup>2, 3</sup>.

#### FOLLICULAR LYMPHOBLASTOMA

Follicular lymphoblastoma, or giant follicular hyperplasia (Brill-Symmers' disease) may be regarded as a variety of

lymphosarcoma and requires no separate discussion of its treatment. It is not as uniformly radiosensitive, in the writer's experience, as is indicated by some reports

### MYCOSIS FUNGOIDES

This peculiar disease is not as yet well placed nosologically. It appears to have some relationship to Hodgkin's disease, to lymphosarcoma, and possibly to lymphatic leukemia. It is characterized by a tendency to show rapid development of bulky fungating tumors of the skin. These are very radio sensitive. In the later stages adenopathy develops which grossly is much like that of Hodgkin's disease, and tumors develop in the lungs, mucous membrane of the pharynx and gastro-intestinal tract, and in the bones. The tumors of the skin will usually show complete regression following a single exposure to filtered low voltage  $x$  rays (500 to 550 r, 140 kv, 3 to 4 mm aluminum filtration, 30 cm distance). Thin superficial plaques, ulcerated or nonulcerated, may yield completely to as little as 300 r of low voltage  $x$  rays, unfiltered, or filtered through 1 mm of aluminum. The nodes and the deeper lesions, as in lungs and bones, should be treated by palliative doses (300 r once to three times) of high voltage  $x$  rays.

### LYMPHOSARCOMA

Lymphosarcoma may be indistinguishable clinically from Hodgkin's disease or from aleukemic lymphatic leukemia. In fact, some writers believe these are but variants of what is essentially the same disease. Certainly there are enough borderline and transitional cases to lend support to such a belief. Except for the not uncommon cases of lymphosarcoma presenting a generalized symmetrical lymphadenopathy like that of lymphatic leukemia (with, at times, a subleukemic blood picture) and the various odd cases of localized lymphosarcomas about the head and neck, this disease, like Hodgkin's disease, characteristically seems to begin in one place, then develops an asymmetrical lymphadenopathy and later becomes generalized. Special clinical features are produced by

those cases in which the disease arises in an antrum, a tonsil, the thymus, the gastro-intestinal tract, or the skin

The fundamental plan of treatment, as in Hodgkin's disease, is determined by asking the question as to whether the disease is localized and therefore offers some hope of cure, or whether it has spread so far beyond its source that treatment must be only palliative. When lymphosarcoma seems genuinely localized there appears to be more justification than in Hodgkin's disease for delivering to the tumor all the radiation that the patient can stand.

A primary tonsillar lymphosarcoma, for example, offers some hope of cure, at any rate, the disease seldom recurs locally after thorough irradiation. In such a case it may be the best form of treatment to irradiate the tumor by exposing alternate sides of the neck through portals not much larger than the tumor to daily doses of 300 r of high voltage x-rays to a total of 3000 to 4000 r to each portal. However, such tumors may be made to disappear completely, with much less discomfort to the patient, and without local recurrence, by exposing the entire side of the neck, treating alternate sides daily, and limiting the total dose to 900 to 1200 r to each side. Appearance of the disease elsewhere, soon afterward, especially in the abdomen and more particularly in the intestine, is so common in these cases of tonsillar lymphosarcoma, that one cannot help feeling that palliation, and not cure, is all that is to be expected, except for the exceptional case. Yet where the disease as far as can be determined is truly localized, no doubt the effort to cure should be made.

Certain cases of lymphosarcoma, simulating advanced gastric cancer, especially at the cardia, may show marked and lasting regression as a result of x-ray treatment.

Surgery is applicable in general only to operable gastrointestinal lymphosarcoma, and offers a few reports of long cures. In other situations surgical intervention for lymphosarcoma is usually a mistake.

When the disease obviously affects widely separated regions the doses used for palliative irradiation are planned in

practically the same way as in generalized Hodgkin's disease. However, regressions tend to be more nearly complete and permanent in the particular fields that are irradiated, the patients, on the whole, can stand larger doses per exposure, and it is perhaps good practice to give 300 to 500 r per dose rather than 200 r as in Hodgkin's disease. These statements are general, and the rule of individualization applies here, as in the other diseases discussed above.

Bone lesions are frequent in lymphosarcoma, as in Hodgkin's disease, and are treated in the same way as in that disease.

### INFECTIOUS MONONUCLEOSIS

More frequently than is generally realized, infectious mononucleosis is mistaken for acute leukemia. No greater pleasure comes to one charged with the care of cases of leukemia, than to be able to assure the parents of a young patient that their child is not the victim of that lethal disease, but, on the contrary, is certain to recover in time. Beginning as an acute or subacute febrile illness, often accompanied by sore throat, presenting a generalized lymphadenopathy, sometimes well marked, and often a splenomegaly, and with a blood count showing a pronounced relative and absolute increase in lymphocytes, it is no wonder that this disease is so frequently mistaken for leukemia. One who is accustomed to seeing cases of leukemia is usually impressed at once by the fact that these patients do not appear ill enough for leukemia. This impression cannot be relied upon, however, nor does it appear that hematologists can always distinguish infectious mononucleosis by the blood smear. The application by Paul and Bunnell<sup>6</sup> of the heterophile antibody reaction appears to offer a reliable laboratory test in differentiating this disease from leukemic and other lymphadenopathies. The test is a simple one, consisting of an agglutination reaction between the patient's serum and washed sheep cells. Stuart and co-workers<sup>7</sup> have recently modified the technic of the test. They conclude that in the presence of substantiating clinical and cytological pictures, serums which cause agglutination in final

dilutions of 1 320 or more may well be considered positive. Serum disease, however, also gives a positive reaction to this test and there is still uncertainty, apparently, as to the limitations of the test, and the fundamental significance of the reaction.

Clinical observation of this disease and all the variants of leukemia furnishes ground for speculation as to the possibility that one individual may react with infectious mononucleosis to a stimulus which in another individual might cause leukemia. It is rather alarming to note how long some residues of infectious mononucleosis, such as adenopathy, splenomegaly, and disturbances in the differential blood count may persist in some patients. It would not be surprising to discover that there are, after all, borderline and transitional cases, linking the two diseases. Therefore, it seems a wise policy to keep patients who have infectious mononucleosis under regular observation for some years after the acute phase has subsided.

As for treatment, rest and general and oral hygienic measures seem most useful. Many of these patients appear to have some slight chronic infection about the pharyngeal cavity. Very small doses of x-rays, 100 to 200 r of high or low voltage, may be of service in some instances, in reducing sluggish lymphadenopathy. Out-of-door life and sunshine seem particularly valuable in promoting recovery in these cases.

#### HODGKIN'S DISEASE

The adenopathy in Hodgkin's disease is characteristically asymmetrical in the earlier stages, and is commonly so throughout the course of the disease. Only rarely does one find a case presenting such a symmetrical lymph node enlargement as is seen in lymphatic leukemia. Usually the nodes are soft at first, tending later to become sclerotic. When the nodes are discovered in the lower part of the neck, the axilla, or groin, it is important to bear in mind that in all likelihood the disease did not actually begin there, but that those nodes are merely signals of a process that began internally, that is, in the mediastinum or the retroperitoneal region. Therefore, a

patient with a group of enlarged nodes in the base of the neck should receive x ray treatment not only to that region, but also to the mediastinum and probably also to the prevertebral nodes of the abdomen

In deciding how to proceed with irradiation of a case of Hodgkin's disease, the first question to be asked is, "Is the disease in this patient really localized to the region where we find it, or is it already generalized?"

If the evidence all seems to indicate that one lymph node area is the sole seat of the granulomatous process, there is justification for heavy irradiation of that area and the immediately contiguous lymph node regions, in an attempt to obtain a cure, or at least a greatly prolonged freedom from activity of the disease

On the other hand, when it is obvious that the disease has generalized, the object of treatment must be to secure the utmost in palliation. This calls for considerable judgment and close observation of the course of the disease so as to avoid doing more harm than good, and also in order not to fail to take full advantage of every opportunity to improve the patient's condition. Patients with this disease vary unaccountably in their tolerance of irradiation, and in the degree of palliation that they show. Therefore, in advanced cases it is wise to begin gently, await results, and to feel one's way along.

In the truly early case, with localization of Hodgkin's disease to one area, surgical extirpation of nodes may be well worthy of trial, provided the operative field and contiguous lymph node areas are promptly irradiated postoperatively. It has frequently been observed that there is seldom a recurrence of any great size in a field that has been well cleaned out surgically. However, cases suitable for this procedure are relatively few, and it is doubtful whether the results are any better in the long run than in cases in which the localized disease is fully treated by radiation alone.

There is no universal agreement on the quality and quantity of radiation to be used in the treatment of Hodgkin's disease. Our own practice has changed considerably within

the past ten years. Formerly we used single exposures of full or nearly full erythema doses of low voltage x-rays (500 to 600 r, 125 to 140 kv, 3 to 4 mm Al filtration, 25 to 38 cm distance). Then we went to high voltage, tending to use half to suberythema doses (350 to 700 r, 185 to 200 kv, 0.5 mm Cu filtration, 50 cm distance). Our recent practice has been to divide the dose of high voltage x-rays so as to give 200 to 400 r per exposure, tending more and more toward the smaller amount, and to repeat the treatment of each field at intervals of from one to three to seven days until a total of 1000 to 1200 r or more has been delivered to each field.

At present, if faced with a case presenting a localized process, in which we hoped to secure a complete and permanent regression, we would prefer to give treatments of 200 r daily or every other day to a total of 1600 to 2000 r to the region involved, and smaller amounts, about 800 r, to the contiguous lymph node areas. I am not convinced, however, that this is the best method, but it seems the best at present, as judged by our experience in producing regression of bulky masses in advanced cases. It does not seem at present that it would be wise to use the large total doses (in the neck, for example, 3000 to 5000 r from each of two portals within a period of three weeks), that are used in the Coutard technic of treating cancer about the pharynx and larynx. An area that has received such a dose cannot safely be treated again, and I believe that the severe disturbance that accompanies these heavy treatments would be seriously injurious to the patient with Hodgkin's disease, who must at all times be kept in the best possible state of nutrition. He cannot afford to undergo the severe discomfort and, in the case of cervical nodes, the interference with taking of food that invariably accompanies the mucositis resulting from such doses.

Even when Hodgkin's disease has become well generalized, with universal adenopathy, large nodular spleen, marked pruritus and fever, it may be possible to obtain such striking palliation by the judicious irradiation of various areas, that the effort required is well repaid. In such cases it seems best

to proceed cautiously with fractional doses (200 to 300, sometimes 400 r) to various areas, the more important areas being treated first. Thus some fields may be given 300 r three or four times, others only once, in a series. The series should not be carried beyond what it is estimated can be tolerated by the patient, and the patient should be allowed periods of rest between the series.

Among the more difficult cases to manage are those in which there is indubitable evidence of disease activity as expressed by fever, loss of weight and strength, itching, leukopenia, or leukocytosis, with or without polynucleosis, but in which no gross foci of disease can be found by physical or x ray examination. Autopsies show two main reasons for the failure to discover the principal seat of disease activity in such cases. A great amount of lymphadenopathy may exist in the mediastinal and retroperitoneal regions without being demonstrable during the patient's life, or there may be a diffuse granulomatous process without the production of gross tumors or lesions, especially throughout the marrow of the bones.

For the above reasons, it is often effective in such cases to irradiate the mediastinal and retroperitoneal groups of nodes, despite lack of demonstrable lesions in those regions, and it may be of some value in some cases to irradiate the bones. Such cases may be particularly suitable for prolonged low intensity irradiation of the entire body either by Heublein's method of continuous exposure, or by intermittent doses. However, when the marrow is diffusely involved, the terminal stage of severe anemia is usually at hand, and it may not be possible to give much more radiation.

After local irradiation has brought about regression of demonstrable lesions, it may be of considerable benefit to the patient to give him a small dose of x-rays over the entire body (by the Heublein method, about 75 r in a period of five days). Prolonged freedom from reactivation may follow this procedure, which presumably exercises a retarding influence on scattered small foci of the disease.<sup>2</sup>

Gross lesions of the bones sometimes osteoplastic, more



frequently osteolytic, are much more common in the course of Hodgkin's disease than is generally recognized. Such lesions about the pelvis or spine or femurs may account for some of the pains that were formerly ascribed to pressure, infiltrative or toxic effects on the peripheral nerves. If such lesions are treated accurately and vigorously, great relief from symptoms and sometimes considerable repair of bone may follow. As a rule divided doses of high voltage x-rays should be used in treating these bone lesions, and should be carried close to the limit of skin tolerance, unless the lesions are so numerous that one must be satisfied with slight palliation, in order not to overirradiate the patient.

Most patients with Hodgkin's disease are greatly benefited by a regime as for tuberculosis. Rest, outdoor life, sunshine and liberal diet are great aids in producing remissions of symptoms and in maintaining long periods of freedom from activity of the disease. Those patients who tend to show a marked gain in weight seem to do best.

**Results in Hodgkin's Disease**—In our series of 125 proved cases of Hodgkin's disease, 15 or 12 per cent survived over five years following the first irradiation. There were in this group on June 1, 1934, 9 patients who were still living. They had survived an average of seven and two-fifths years since beginning treatment, and had an average total duration of life since onset of symptoms of nine and one-half years.

#### CARCINOMATOUS LYMPHADENOPATHY

The treatment of carcinoma in lymph nodes is too extensive and varied a subject to be considered here in detail. Depending on the origin, the location, and extent, the treatment varies widely. Thus, the treatment of a node of Virchow in the left supraclavicular space, involved by carcinoma originating at a distant point, such as the stomach or testicle, is an entirely different problem from the management of cervical nodes to which an intra-oral carcinoma has metastasized, or from the treatment of axillary nodes, to which a mammary carcinoma has spread. The diagnosis is usually—but by no means al-

ways—obvious in the light of careful physical examination. Carcinomatous nodes are characteristically stony hard, but may be deceptive by their comparative softness or by accompanying evidence of inflammatory changes.

The choice of treatment lies between (1) surgical removal, with or without implantation of radon seeds in the tumor bed, and with or without pre- or post-operative external irradiation, (2) surgical exposure to permit accurate insertion of radium or radon, (3) external irradiation alone. If carcinomatous nodes are to be treated by external irradiation, the best method appears at present to be the divided dose technic with the radium pack at the greatest practical distance (10 to 15 cm), or with  $x$  rays produced at the higher voltages (200 to 700 kv). In  $x$  ray treatment, 300 to 400 r may be given daily or every other day to a total of 4000 to 5000 r. The field of exposed skin should be kept as small as possible, without excluding some of the tumor, in order to avoid excessive local and general reactions.

Occasionally there is encountered a generalized carcinomatous lymphadenopathy. In such cases it is not infrequently impossible to discover the primary tumor, except at autopsy. Such cases may simulate Hodgkin's disease or other noncarcinomatous lymphadenopathies. The fact that the disease is a metastasizing carcinoma may not be recognized until biopsy material is examined. One such case was seen recently.

A stuporous woman was admitted with a generalized asymmetrical lymphadenopathy which passed at first as probably being Hodgkin's disease, and might have continued to be so regarded, except that the nodes seemed too hard for comparatively early and nonirradiated Hodgkin's nodes. Biopsy of an inguinal node showed adenocarcinoma, the origin of which could not be determined from the slide. The primary site could not be found while the patient lived. At autopsy the primary tumor was found in the tail of the pancreas.

A few years ago another patient was regarded as having a mediastinal tumor, probably a highly cellular carcinoma of the thymus. This diagnosis was based on the clinical features,

the biopsy of a cervical node and the response to treatment. After a course of over a year, he developed several widely scattered metastases, some of which were very painful, and he committed suicide. Autopsy showed a carcinoma of the tail of the pancreas.

As a rule, carcinomatous nodes will show little or no response to a dose of  $x$ -rays that would be sufficient to cause complete or subtotal regression of Hodgkin's nodes. Thus, if for some reason a biopsy is not done,  $x$ -ray treatment may be used for a diagnostic test.

Naturally, if it is found that a generalized adenopathy is due to carcinoma, it is a waste of effort to attempt radiation therapy of the whole disease. Irradiation of the entire body is of very little help in such a condition. It may, however, be advisable to use moderate local doses of  $x$ -rays in selected cases to relieve pain or swelling in some particular region.

#### MYELOGENOUS LEUKEMIA

The typical case of chronic myelogenous leukemia is characterized by massive splenomegaly, myelemia, and a notable absence of external adenopathy. Occasionally cases are seen in the earlier stages, or following irradiation, with comparatively slight enlargement of the spleen, or even without demonstrable splenomegaly, or with equivocal blood counts. A history of long-standing fatigue is common, as is some evidence of hemorrhagic diathesis, particularly a tendency to show ecchymoses on slight or no injury, or, in women, menorrhagia. A more pronounced hemorrhagic tendency, shown by nosebleeds, bleeding from gums, conjunctival hemorrhages, or petechiae, is a bad omen, as a rule. The presence of definite external adenopathy usually indicates a more acute type of case. The presence of an acute infection, as of gums, throat, sinuses, respiratory tract, or skin and subcutaneous tissues, is also unfavorable. A red cell count below 2,000,000 is usually a bad sign. The more acute the symptoms, the more commonly will pronounced sternal tenderness be found. Gross lesions of bone are rare.

One of the earliest therapeutic uses of  $x$ -rays, aside from

the treatment of skin diseases, was in myeloid leukemia. Even with the early technics, using gas tubes, low voltages, little or no filtration and short target skin distances, when penetration of the rays was very slight, some good temporary results were obtained. Radium in small quantities, applied close to the surface of the body in multiple portals over the spleen, also brought about palliative results. In the earliest years the long bones were commonly treated in addition to the spleen, but later there arose a rather general feeling that the results were as good or better if only the spleen were irradiated. At Memorial Hospital the practice became established of applying the radon pack over the anterior surface of the spleen, in single doses, rather massive for this distance, such as 6000 to 8000 millicurie hours at 6 cm. distance, or 10,000 millicurie hours at 10 cm., filtered by the equivalent of 2 mm. of brass. Such doses caused marked constitutional reactions as a rule, but resulted almost routinely, in favorable cases, in a regression lasting from three to eighteen months. A few patients, in whom the acuteness of the process was not recognized, succumbed rapidly, evidently as a direct result of overdosage. During this time the usual practice elsewhere was to apply occasional small doses of x rays or radium to the spleen, not attempting to obtain a rapid regression.

The technic now in use at the Memorial Hospital in irradiation of the spleen for myeloid leukemia was devised about eight years ago. It was an attempt to combine the advantage of rapid regression of the disease observed following massive radon pack dosage with the advantage of minimal disturbance of the patient by divided dosage. It was arbitrarily judged that the delivery within a period of six days of equal daily doses of x rays produced at 140 kv., filtered through 5 mm. of aluminum and used at 38 cm. target skin distance, to total a mild erythema dose (now measured as 600 r) should accomplish about the same result as the single radon pack dose of 8000 millicurie hours. It worked. The same sort of rapid regression followed. The patients generally no longer needed to stay in the hospital, as they were spared severe constitu-

tional reactions Within a week their cycle of treatment was finished, and they did not need to be treated again for from three months to a year or longer Such a division of dosage, using only 100 r a day, permitted the use of several subsequent cycles of treatment over the same field, with scarcely appreciable resultant changes in the skin Moreover, as experience was gained, this method was found to have a flexibility that permitted an adjustment of the number of treatments comprising a cycle, or the dose per treatment, depending on the features of the case, so that the advantages of the concentrated, divided dose method were retained in all cases amenable to irradiation This was one of the earliest applications at Memorial Hospital of the concentrated divided dose method, which has more recently been applied in much larger doses in the treatment of several varieties of malignant tumors, following the lead of Coutard

For the more acutely ill patients the daily dose to the spleen may be reduced to 50 or even 25 r The typical case may be carried along for a year or more solely by such cycles of x-ray treatment of the spleen, the cycles being repeated at intervals of three to six months The exceptional cases may be carried for four to seven years At present we tend to return to the former practice of irradiating the bones For this purpose we routinely employ 200 to 300 r of high voltage x-rays, generated at 200 kv, filtered through 0.5 mm of copper and used at a distance of 50 cm The areas usually treated are the proximal ends of all the long bones, the entire spine, and the sternum Treatment of the bones seems to be of particular value in those cases in which there are pains in or about the bones, or joints, or in which the response to irradiation of the spleen is not satisfactory

The results that were found to follow the use of x-rays or radium in the treatment of myeloid leukemia led to a general disregard of the palliative effects of arsenic, and it was not until the report of Forkner<sup>8, 9</sup> that, in this country, at least, renewed attention was paid to the merits of this ancient remedy

In recent years we have begun to use arsenic, not as relentlessly as Forkner did in his reported cases, in which he was testing its effects as compared with the results of irradiation, but in more guarded doses. Starting with 3 minims of Fowler's solution three times a day we increase it by 1 minim per dose each day until the patient is taking about 10 minims three times a day. The dose may then be gradually reduced to the initial amount, or arsenic may be discontinued, and the patient may be allowed to go a week without arsenic. Then the same cycle of ascending dosage is repeated. There is some evidence to show that arsenic may improve the response of these cases to subsequent irradiation, when they have shown a tendency to be refractory. We restrict its use almost entirely to the intervals between cycles of x ray treatment.

There is perhaps no other disease so susceptible to a variety of adverse factors. We have seen in two patients an acute exacerbation with rapidly fatal termination following closely upon the death of a near relative. Rest and avoidance of fatigue, both mental and physical, is of prime importance in the care of the leukemic patient. Exposure to sunlight, as recommended by Naegeli, is undoubtedly beneficial.

Moderate exposure to sunlight is helpful, and occasionally is of service in checking a hemorrhagic tendency to combat which it is our custom to prescribe, in addition, a high vitamin intake and 30 to 60 grains a day of calcium lactate or gluconate. In the presence of a hemorrhagic tendency more than of slight degree one must be cautious about using radiation.

No greater mistake can be made in treating the leukemic subject than the overenthusiastic surgical attack upon supposedly causative foci of infection such as teeth, tonsils, and sinuses. They may have been causative in the past, but surgical meddling with them in the presence of an active leukemia may be and often is disastrous. Following extraction of teeth bleeding from the gums may continue for a week. Following antrotomy infection may increase and spread, the dreaded hemorrhagic tendency may appear, and the case may

become converted into an acute leukemia with the picture of sepsis. However, in the presence of an actual gross focus of suppuration, some conservative measure of drainage with a minimum of trauma is usually indispensable.

What good are transfusions in leukemia? Despite occasional reports of marked temporary benefits, particularly in children, it may safely be stated that, as a rule, transfusions are valueless, and in some instances seem harmful. One seldom thinks of using transfusion in chronic leukemia. In the acute forms, either true acute leukemia or the acute exacerbations of the chronic form, with fever, high metabolic rate, a hemorrhagic tendency, and frequently signs of infection, one is always tempted to advise transfusion. It is frequently difficult to decide whether the acutely ill patient is going to die shortly despite all therapeutic measures, or whether there is a chance of bringing about a remission. The report of Gloor<sup>10</sup> on the apparent cure of a case of acute myeloblastic leukemia by a mixture of irradiation, injections of arsenic, intravenous injection of mesothorium, transfusions, and administration of iron, is an encouragement to attempt to treat cases that seem hopeless. However, one must be particularly cautious in using x-rays or radium in the acute cases. Death may follow within a few hours following the injudicious application of doses that might safely be used for the chronic cases.

**Results**—Hoffman and Craver,<sup>11</sup> in 1931, published the results of a study of the duration of life in 82 cases of chronic myeloid leukemia, as affected by irradiation, comparing their figures with those of Minot. They found the average duration of life after the beginning of treatment to have been two and six-tenths years. They concluded that radiation treatment caused an average increase of about ten months in the duration of efficient life, a period of usefulness and comparative well-being which the patient could not otherwise hope to enjoy.

#### PERSISTENT ENLARGEMENT OF THYMUS IN INFANTS

A common history in these cases is that since shortly after the birth of the child the mother has noticed that its breathing

has been abnormal. This varies from slight noisiness such as would be produced by a little mucus in the pharynx accompanying a cold, to pronounced degrees of stridor, sometimes associated with attacks of cyanosis and apparent unconsciousness. It is practically never possible to elicit physical signs of the enlarged thymus in these young infants. The interpretation of  $x$  ray films is often a matter of opinion, as to whether the mediastinal shadow is wider than normal. It is well known that similar symptoms are found in many infants, in whom no enlargement of the thymus can be demonstrated. Conversely the thymus may appear enlarged in others who do not have symptoms. Especial care must be taken to exclude a congenital heart lesion, which may in some cases give rise to a widening of the mediastinum located apparently above the heart and thus lead to an erroneous diagnosis of enlarged thymus. Particularly if the enlargement is mostly unilateral should one be cautious in accepting thymic enlargement as the cause. It is possible, of course for thymic enlargement and congenital heart disease to coexist. There are evidently gradations between simple hyperplasia and true neoplasms of the thymus in infants. In the majority of cases, both the symptoms and the enlargement of the gland will disappear following small doses of  $x$  rays, but in a few instances the symptoms or the enlargement, or both, persist. In the latter cases just what relation there may be to the cases of enlarged thymus associated with leukemia in children remains obscure.

The treatment of the ordinary case calls for one, or not more than a few applications of small doses of  $x$  rays. Seventy five to 150 r of low voltage  $x$  rays (factors 140 kv, 4 ma, 3 to 4 mm Al distance 25 to 30 cm) will suffice, but because of the difficulty of holding a young infant in place under the usual unprotected type of low voltage tube it may be much easier and just as effective to use 75 to 100 r of high voltage  $x$  rays (factors 200 kv, 4 to 30 ma, 0.5 mm Cu, distance 50 cm). As a rule, such treatment is followed by prompt relief from symptoms and eventual shrinkage of the gland.



## SUMMARY

In the foregoing pages, the writer has recorded his current preferences in modes of treatment of the more important forms of lymphadenopathy. The range of the various subjects considered is so wide as to preclude a detailed discussion of exceptions and complications. Until further knowledge and experience are gained the treatment of all of these diseases must remain largely empirical.

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## CLINIC OF DR HARLOW BROOKS

### BELLEVUE HOSPITAL

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#### THE FAILING HEART ITS RECOGNITION AND MANAGEMENT

You have asked me to speak to you on the subject of the recognition and management of the failing heart. You are aware that cardiologists now classify this condition into certain groups, theoretically based on the apparent gravity of the condition. Prognosis and definite classification are, however, most difficult things to ascertain and for the clinician I think it far more important that we consider the condition from the standpoint of its probable pathology, for this is exceedingly variable and differs in each individual instance. Without at least a mental picture of the pathology most probably concerned in any special case, it is in my opinion impossible adequately to outline treatment. So you must bear with me for a few moments while I try, very briefly to present this aspect of the condition.

We must recall that the failing heart may be caused by many conditions and presents a very varied pathology. The basis of disturbance may be by no means always centered in the heart, though more frequently this is the case. One must bear in mind that many instances originate from a primary valvular defect from whatever original origin, perhaps from a primary defect of the heart muscle. Then, again, though much less frequent relatively, the primary disease may have originated in an arrhythmia which, through its abnormality, has exhausted the heart. Of late we have perhaps somewhat underestimated the frequency with which cardiac failure is followed from disease or thrombosis of the coronary

nonetheless is one of the very most frequent causes of heart failure. Pericardial disease, either an acute exudative process or perhaps an old adhesive one, may also be the cause of origin of a failing heart.

We are very short-sighted, however, if we look to the heart exclusively for the fault, because heart failure in all cases involves all the tissues. It is here, then, that the judgment of the internist or general practitioner becomes of particular worth. The high frequency with which hypertension causes cardiac failure must be considered. It may be perhaps of long standing, perhaps of but recent development, perhaps essential or possibly secondary to long-standing renal or other disease, as from a widespread endarteritis, an atheroma, or the like. There can be no doubt, in view of our recent studies of hepatic disease, that cardiac defects may follow from them, though, as all practitioners know, it is much more frequently the other way about. Overwork, especially unaccustomed overwork, becomes an occasionally important factor in the development of heart failure though I think it operates only in the presence of some essential defect either in the heart itself or within the capillary or arteriolar bed. Hemic disease, particularly the anemias, is very frequently the essential background of a failing heart. Perhaps most important of all—since it is probably the most common of all and in many instances among the most insidious and unexpected of all—are the infections. Certain of them, it is true, are more prone to invite heart failure than others, such as, for example, diphtheria, influenza, pneumonia, typhoid fever, and others. Some of you are wondering why I have not placed rheumatic fever as of very high frequency in this class. There is no possible doubt as to the very common dependency of heart failure on rheumatic disease either acting on the valves or on the muscle, but I am not at all certain that we can correctly class rheumatism as an infection. This may seem heresy, but few experienced practitioners feel otherwise. There are, of course, other factors that have a similar effect but I think that I have mentioned the more frequent

I have felt it necessary to consider the pathology concerned for the reason that treatment can be correct and adequate only if based on a knowledge of the pathology, though, of course, it is in many cases impossible to ascertain it accurately but only tentatively and for the purpose of institution of treatment. In most instances, however, the character of the symptoms and signs serves to indicate fairly definitely the type of pathology.

Thus, in the failures due to acute infections as in rheumatic fever, pneumonia, diphtheria, influenza and the like, the history of the case together with a rather less florid onset, serves to suggest very definitely the character of the basic pathology. In cases due to coronary thrombosis, the sudden onset, the faint and distant heart sounds, perhaps the sudden development of a pericarditis, the usual absence of marked cyanosis, a degree of shock out of proportion to the immediate appearance, and commonly the presence of pain and a drop in blood pressure, are indicative.

Overstrain, when accompanied by actual valve or aortic rupture, is accompanied by tremendous shock, extreme arrhythmia, and blood pressure variations. When due to moderate giving way of the muscle, and without marked actual lesions, the symptoms are more those of exhaustion, the heart sounds are distant and faint whereas when actual rupture has taken place one finds new and inconsistent heart murmurs, often of great intensity.

Chronic failure, that is, failure that develops slowly and often very insidiously, presents, of course, a very different aspect, perhaps occurring most strikingly and most commonly in chronic valvular disease, atheroma or old age with its wide spread and extensive lesions. It is very similar to the picture of rheumatic carditis of the chronic type. A quite similar picture develops in the chronic type of muscle disease such as one finds in typhoid fever, chronic overstrain as from hypertension, old renal or hepatic disease, malnutrition, the anemias, and the like.

The symptomatic picture of acute failure is usually very

dramatic and obvious Collapse and shock are perhaps the most brief but highly descriptive terms that may be applied, but with these—except as we have mentioned already in acute coronary disease—cyanosis and venous congestion are almost always present, often in extreme degree Tachycardia is the rule and most commonly with various forms of arrhythmia, often of a very incoherent type and form Hypotension, at least a relative hypotension as compared to that previously present, is the rule Most significant of all is a greatly lowered pulse pressure and, as additional evidence of the same state, a decreased output of urine, often complete anuria Mental torpor is usual, often extending into true coma, likely to be confused with that of uremia Dyspnea and orthopnea are striking symptoms, and, of course, the physical signs of more or less pulmonary edema

Capillary extravasations, infarctions and other peripheral manifestations of an inadequate driving power from the heart are often present Pain, usually constant, boring and associated with a sense of precordial weight, is frequently present Quite unlike the pain that occurs in angina pectoris, for it is rarely reflected, it is not paroxysmal but constant and heavy, not darting but squeezing and gripping

Where the failure has been of slow onset, that is, in cases of chronic type, a very different type of picture develops, and one much more likely to escape correct recognition, because of its ordinarily slow onset which may very well be described occasionally as insidious, especially in the less aggressive forms of the condition

One of the less frequently recognized symptoms, especially by the patient himself, is exhaustion and loss of strength This state may exist often for a very long time without the appearance of other signs or symptoms likely to arouse the apprehension of the patient Sooner or later dyspnea appears, first only on marked exertion, later it develops on very slight provocation With this often appears a striking orthopnea The patient notes that he requires more pillows for comfortable rest at night He becomes, as he complains, asthmatic

Cyanosis is frequently very slight, but it may be marked, particularly in long standing and now decompensating valvular defects, but edema is almost always present and it is particularly evident in the pendant portions of the body

Pulmonary edema is frequent, but ascites is much more so and more frequently of marked degree. More or less alteration in arterial tension is usually present and there is a definite tendency in practically all instances for the pulse pressure to become less and less. At about this period, irrespective of whether the primary lesion is of the muscle, of the valves, or of coronary origin, or if perhaps due to pericardial adhesions, the arrhythmias appear and it is common for the longer standing cases to show a bradycardia, or at least a tendency toward it, though in the immediately terminal stage tachycardia is the rule.

Patients of this chronic condition are very commonly seen in the gastro-intestinal clinics because of the frequency with which they suffer from flatulence, nausea, and distress after eating, and from symptoms in general which they define as "indigestion." These symptoms are due to enlargement of the liver, to congestion and edema of the gastro intestinal mucosa, to ascites, and the like. The symptoms are then entirely secondary and misleading in their natural lay interpretation, and, all too frequently, the careless doctor may arrive at the same erroneous conclusion. Physical examination, of course, discloses the true nature of the essential defect unless, perchance, the physician be so highly specialized that he fails to achieve the general perspective of the regular practitioner who but views symptoms and disease as corporeal in the main and not visceral only, as the narrow specialist feels that disease should be.

Jaundice frequently appears, due either to congestion of the hepatic venules, or in long standing instances, to the fibrosis that occurs in the interstitium as a result of chronic liver congestion. Jaundice of a hematogenous type also may appear from the breaking down of the blood in the peripheral channels. Similarly the urine is reduced in quantity, its specific gravity

is customarily increased, and it contains blood cells, casts and other elements indicative of defective renal action—even nitrogenous retention in the blood serum may be found, and the picture of a kidney defect further suggested

Cough appears, especially on slight exercise, and a rusty and blood-containing sputum may be expectorated. Considerable areas of almost inflammatory character appear in the lung as a result of mingled edema and congestion of lung tissue. Precordial distress may be marked or slight. In conjunction with other evidences of peripheral venous and capillary congestion, hemorrhoids frequently appear and, again, our unhappy patient may consult a specialist who may perhaps treat this sign, and not the disease causative of it. Not that the hemorrhoids do not merit treatment, for they are frequently most distressing, but local measures must be supplemented by general measures if the patient is to receive real medical justice.

Practically, there is no function or part of the body that does not suffer in the chronic case of cardiac inadequacy. Anemia develops, menorrhagia during menstruation, even mentality is slowed, headache appears, and mental effort becomes almost as defective and slowed down as more crudely physical effort. Eyesight and the other special senses wane. This is a picture, then, that demands the attention of the doctor, and not of the myopic specialist. It is these cases of chronic or slowly progressive heart failure that most frequently escape observation, acute cases of heart failure admit of but relatively little opportunity for lack of recognition.

You have noticed, no doubt, that I have said very little as to methods in the diagnosis of this condition. My neglect has been purposeful for I am certain that this group of general practitioners will have but little difficulty with this phase if you but recall the mechanism of the process concerned in the failing heart. I have attempted rather to build up a picture of how it all comes about, feeling that if this is recalled diagnosis will require nothing beyond the skill of any of you. As a matter of fact, inspection alone is quite sufficient in most

instances for an entirely satisfactory working diagnosis in these important cases. With the history, the findings of inspection, ordinary auscultation and percussion, there is small probability that you will be misled in diagnosis. Wherever question, doubt, or confusion from complications appears, you all know the utility of the fluoroscope and of the x ray plate. You have, of course, examined the urine. You will appeal sometimes, though not very frequently, to the electrocardiograph, particularly when the question of exclusion of coronary disease comes up. Perhaps you will wish to study the retina with the ophthalmoscope to exclude or confirm renal or hypertensive disease, but in the main you will find that the study of your patient as a whole will give you all the information necessary for the correct and immediate treatment of your patient.

There is nothing very new, mysterious, or remarkable about the treatment of these cases. You will accomplish all that anyone may do for these patients by the application of long known and well-established methods of treatment, modifying your methods in every instance by the needs of each special patient, for, as in most other types of disease, no cases are identical, and we physicians must not fail to recall that we are treating biological individuals and not mere machines.

Acute cases of cardiac failure demand great promptness in treatment, as a rule. Yet nearly all of them rate at least a working hypothesis of the basic pathology concerned. An acute coronary thrombosis, for example, should certainly not receive the treatment desirable in acute dilatation from an old valvular defect.

When cyanosis and dyspnea are marked, most acute cases profit from venesection. As to the amount of blood that should be abstracted, the best guide is furnished by the relief that follows: as soon as the cyanosis and dyspnea are relieved, no more blood should be taken. The distress—mental and physical—of the patient is most promptly relieved, as a rule, by a hypodermic of morphine and this is very unlikely to do harm, irrespective of the cause of failure. There are, also, very few



instances in which it does not give real benefit, and that promptly Morphine contributes, moreover, to that first principle of medical practice It gives rest, which is particularly desirable in cases of cardiac failure, and added comfort

This essential of rest brings up the question of posture It is natural for us to put these patients to bed immediately, and to insist on a prone posture This is often a great mistake, however Acute cases in particular are often much more relieved when seated in a comfortable chair or in an inclined position in a Gatch bed, or the like If shock is marked, heat is often most desirable, applied just as you would in any other condition of shock, but with as little manipulation of the patient as possible Too meddlesome diagnostic measures should certainly not be attempted at this stage

If the pulse is regular and fairly full, digitalis should probably not be given Only in very exceptional circumstances, in cases in which an acute coronary lesion is suspected, should it be used, if arrhythmia is marked and dyspnea definite, it should be given, however, intravenously or intramuscularly, and in such doses as to be effective Caffeine, best given as soda benzoate hypodermically, is often very effective, especially in those cases that are in shock It has the advantage of being without contraindication when coronary thrombosis has taken place It in no way replaces morphine, however, and there is no contraindication between these two excellent drugs in cases of acute heart failure

Adrenalin is often very effective, given better hypodermically than intravenously, always depending on the reaction of the patient Except when hypertension is marked, it is not contraindicated, even in coronary disease Other drugs are to be utilized as the case may indicate Strychnine is no longer fashionable but is occasionally very useful, especially when there is deficient muscle irritability in the heart, it is often a very valuable adjuvant to digitalis Atropine is often highly beneficial (always depending on the reaction of the patient), especially when pulmonary edema is present

Intracardiac medication is occasionally indicated in cases

in which other and more ordinary measures fail, in fact, in these emergencies, a very large group of drugs is advisedly employed because very many of these cases are first seen in extremis and almost anything promising even mere hope may be attempted. Intravenous saline, glucose and other similar measures may seem indicated. Ouabain has acted apparently well with me on several occasions, its use depending on the reaction of the patient, strophanthin and others of the less familiar drugs, also, the same condition applying. Some cases are greatly relieved by oxygen, preferably given by the tent method, or through the nasal catheter. The resolute physician will persist in his treatment of these cases, though failure is more frequent than success, except where acute failure appears in chronic lesions, in which cases prognosis is usually much better than in instances that develop acutely.

As I have attempted to point out to you, the appearance of frank chronic cardiac failure may be very slow and so insidious that even the attending physician may scarcely be aware of the period when active treatment becomes imperative. It is much better in cases that are subject to the pathology in which a chronic cardiac failure is likely to appear, to insist on routine examinations, and to begin treatment, as it were, prophylactically. This is particularly true in old age, when the early use of very small doses of digitalis over very long periods of time frequently prevents a failure of the heart. I have carried out this method over periods of twenty years in instances of chronic myocardial fibrosis, chronic rheumatic heart, and in valvular defects of almost any sort. Very small doses of an effective preparation may entirely suffice, perhaps no more than a grain of a good leaf daily for a man of average weight will serve to keep him in good health and comfort for very long periods while a discontinuance of this minute dosage is soon followed by evidence of heart inadequacy.

Digitalis is so remarkably effective in very many cases of chronic heart failure that it not only relieves the patient but also actually cures many cases of malignant therapeutic nihilism. The dosage should not conform to any rules as to body

weight, these are really devised to indicate the limits of safety Digitalis in cases of chronic or impending heart failure should be given experimentally, as it were, until it is determined what is the most satisfactory dose and preparation for the particular case under observation This was the method advised by my own teacher of pharmacology, many years ago, and at that remote time Cushney was widely criticized because he gave "digitalis until digitalis effect was produced " Modern studies of this sturdy drug have added but little to the clinical use of digitalis as taught by this pioneer pharmacologist So I say determine by therapeutic experiment if digitalis is effective in any patient, determine by the same intelligent manner the form of the drug and the most desirable dosage You will find a tremendous variation in these matters, as you older practitioners well know

It is difficult for me to stop talking about digitalis, so enthusiastic am I about its benefits in most cases of chronic heart failure I shall add only that the skill of the physician in its management and a careful study of its effects on each individual patient are necessary if best results are to be attained Broken periods of administration are very effective in many, but by no means in all, cases of this kind

You have noted that in the treatment of this condition I have placed the use of digitalis even before physical methods of prophylaxis and care This has been by design Rest is, after digitalis, our best method for the prophylaxis and treatment of chronic heart failure Again, however, there may be too much of a good thing, too large a dosage of rest as of other medicaments This, too, must be determined by therapeutic experiment I am in the habit of insisting on more than a usual amount of rest for all cases of tentative heart failure as a matter of prophylaxis In those frequent cases in which it is necessary for the patient to continue his occupation in spite of his infirmity I like to insist that he spend his Sundays in bed, resting from Saturday afternoon until Monday morning It is very gratifying to note how much may be accomplished by this logical and inexpensive rest cure without, in any serious

way, interfering with the patient's obligations of life. Those of us who have to do only with hospital cases are too likely to forget that mental peace and minimization of worry are large factors in rest and recovery. When the patient, by such methods as I have just mentioned, can be kept secure in his livelihood and, at the same time, obtain the adequate rest which his condition necessitates, we add very much to his longevity and to his content in life.

Rest, particularly rest in bed, however, may be given in too large dosage for the patient's best welfare. In most chronic cases of failing heart, there comes a time when more, though always very temperate, exercise becomes necessary, for the heart muscle like every other muscle requires exercise lest it degenerate and become less efficient than before rest treatment. We must, then, not keep our old cardiac cases too long in bed, or, if this is imperative because of the gravity of the case, we must substitute for exercise, massage, passive movements, and the like. Above all, in the physiotherapy of the chronic failing heart, we must individualize our treatment.

There is so very much to be said concerning physiotherapy in the chronic cardiac that one finds it difficult to stop. There can be no doubt in your minds, surely, as to the value of hydrotherapy, of the regime of the various health resorts, in the treatment of these cases. We Americans should remember that we have more vitally valuable springs in this country than in all of Europe. Indeed, it is said that Yellowstone Park includes in its limits more really therapeutic waters than all of the rest of the world. But we have allowed Europe to monopolize in this type of treatment, greatly to our and to our patients' disadvantage. There is much more that I wish I might discuss with you in this matter of physiotherapy, but we must not neglect drug treatment. There is none among you experienced practitioners who does not realize the value of drugs, even of other drugs than the digitalis group, in this class of disease.

The purgatives and laxatives have a distinct rôle in nearly all instances of the chronic failing heart. The dehydrating

value of the salines in this class of disease has long been recognized. Magnesium salts, sodium phosphate, and others of this class are of primary value especially in hydremic cases. We should not forget the use of calomel, properly applied, as, for example, in the old Fothergill's pill, three to six daily one day out of each week, as valuable in these cases today as eighty years ago. Have you forgotten that calomel, properly given, is an excellent diuretic as well as a cholagogue and cathartic, perhaps you prefer the modern salyrgan.

The value of diuretics in many of these cases is evident to all of you. Such drugs as caffeine and theosine are frequently imperatively indicated. Please recall that all drugs of this group have, also, a very certain stimulative action on the heart muscle, but you must remember, too, that they are cerebral stimulants as well and that when given indiscretely, they add to insomnia, restlessness and irritability. Please recall, also, that two of the most potent preparations of caffeine and theosine are coffee and tea. These drugs are almost all coronary vasodilators and the old and pharmacopeal forms are, in the main at least, as valuable as the numerous new and expensive types now on the proprietary drug market.

Alcohol is a sedative, not a stimulant, but it may nonetheless be discussed along with caffeine and theosine because of the agreeable forms in which it, too, may be prescribed. Alcohol, especially taken at night with the evening meal, or on going to bed, particularly in cardiac disease in the aged, is a valuable drug and an agreeable condiment, producing in suitable cases an euphoria more definitely and more constantly than any other drug at our command. Sedatives are often indispensable in cases of failing heart. The bromides and chloral hydrate have not been displaced by any of the newer hypnotics. The fear of morphine has been so overcultivated by lay organizations that many physicians have forgotten that opium, particularly the older forms, may be given advantageously for months and even for years, if administered under competent medical control. It is a very cruel and inhuman thing to withhold opium in cases of this character when the

drug is medically indicated. We all agree, however, that this is not a drug to be put in the hands of the amateur, neither, for that matter, are the numerous other sedatives, hypnotics, and analgesics that are frequently necessary in the treatment of this and many other diseases.

Vasodilators have been mentioned, in part, under the caffeine and theosine salts, but some cases demand vasodilators of more positive character, such as the nitrites, nitroglycerin, sodium nitrite, erythroltetranitrite, and others. As a rule, these drugs are more highly efficient for symptomatic usage in special instances rather than as a matter of routine for the reduction of hypertension in which their continued exhibition is usually more harmful than beneficial, but especially in the chronic failing heart we must always recall that symptomatic treatment is proper whenever it adds to the comfort of the patient. We must not forget, then, that the symptoms of the condition, such as those of the gastro-intestinal tract, must be given a hearing and, insofar as is possible, mitigated by diet, physiotherapy, and by drug use whenever necessary.

In hydremic cases, obviously fluids should be restricted, the highly salt foods must be curtailed, sweating favored, and the saline laxative prescribed. It may be necessary to give diuretics. Urea, salyrgan, sodium citrate, and diaphoretics, or, at times, atropine. It may become necessary to resort to Southey's tubes or to evacuate pleural or peritoneal exudates.

I apologize for having taken up so much of your time on a subject of which I know that every experienced practitioner is well qualified to manage, but it does no harm occasionally to review our knowledge. There is one point which I am most anxious to make very positive to you. In our treatment of the failing heart, we must above all else treat the patient as a whole and as an individual, for it is the whole person that is sick, not just the heart, and not alone the body, but the mind of the human, also. Each case must be considered as a personality, as well as a mechanism, out of order.



## CLINIC OF DR ERNST P BOAS

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#### THE TREATMENT OF EARLY HEART FAILURE

THE circulation by its constant flow maintains the exchange of oxygen, carbon dioxide and other metabolites between the lungs, the alimentary tract, the tissues, and the excretory organs and acts as a carrier of the chemical internal regulatory mechanisms of the body. The efficiency of the circulation depends in large measure on the functional integrity of the heart, although other elements such as the vasomotor control of the arteriocapillary venous mechanism, and the blood volume play important roles. Heart failure results in circulatory failure and manifests itself by signs and symptoms arising not alone in the heart, but in other organs such as the brain, the lungs, the liver, the kidneys whose functions are impaired by the inadequate circulation. The earliest indications of heart failure, before structural alterations in organs have taken place, are the subjective symptoms of dyspnea, palpitation and precordial pain. In the first stages of failure these arise only on effort and the degree of failure can be gauged by the amount of effort required to provoke symptoms. When symptoms of heart failure occur at rest, or when signs of congestion of the lungs, the liver, or the kidneys have appeared, failure is far advanced.

Dyspnea, palpitation, precordial pain, though common signals of heart failure, may also occur in functional neurogenic disturbances of the circulation or in severe anemia. To diagnose heart failure then it is necessary to associate these symptoms with a cardiac lesion that can give rise to them and



with physiologic disturbances of the heart such as alterations in rate or rhythm. An individual has heart failure when, as a result of a heart lesion, he is unable to carry on his accustomed activities without symptoms of circulatory failure.

We are so habituated to associate heart failure with signs of congestion of the lungs and liver, or with edema that we are apt to overlook its presence in the earlier stages. A patient with active rheumatic myocarditis, or with angina pectoris may have heart failure just as truly as one with congestive failure and auricular fibrillation. Although the principles underlying the treatment of heart failure apply to all forms of heart disease, their application to the particular forms of heart disease is sufficiently varied to warrant separate consideration of the different types of heart disease.

#### RHEUMATIC HEART DISEASE

Heart failure complicating rheumatic heart disease occurs as a result of an active rheumatic carditis, or of the onset of a cardiac irregularity such as auricular fibrillation, or from a gradual weakening of the heart muscle that has labored for years to overcome the handicaps engendered by progressive valvular deformities. At times such heart failure develops suddenly after overexertion.

**Rheumatic Carditis**—In this condition heart failure is the direct result of an active inflammation of the heart muscle. Signs and symptoms of heart failure may not be apparent in many patients with active rheumatic infection of the heart, but, as a rule, palpitation and dyspnea on exertion, often with sticking precordial pain are observed, and almost invariably the pulse is rapid. Experience has shown that in the overwhelming majority of individuals with rheumatic fever, the carditis persists as long as the systemic infection. It is unnecessary and unwise, therefore, to await manifest evidences of heart failure in these patients, but rather to assume the existence of heart failure in every patient with rheumatic infection and to treat him accordingly. There is no specific therapy for rheumatic fever, salicylates, although they reduce

fever and joint swellings, do not influence the course or duration of the disease, and have no effect on the cardiac infection. Treatment, therefore, is directed to sparing the heart and maintaining its efficiency while awaiting the subsidence of the infection. The most important measure is rest. Bed rest must be enforced until the complete arrest of the infection. In the earlier stages, particularly when a rapid pulse, changing murmurs, or a pericarditis proclaim serious invasion of the heart this cannot be too complete. The patient should be as immobile as possible, he should be turned in bed, and fed and waited on in every way. As improvement occurs these precautions may very gradually be relaxed. It is not easy to know when the infection has been eradicated and when the patient may leave the bed. The best guides are the temperature, the heart rate, the white blood cell count, and the sedimentation rate of the red blood cells. When all four are normal and remain normal for two to three weeks it is fairly safe to assume that the active infection has terminated, but even after this period the temperature and pulse rate must be followed for several weeks for recrudescences are not uncommon. Restoration to normal activity must be very gradual and guided by the response of the heart to effort.

The diet must be liberal even during the acute febrile period. Rheumatic fever, like tuberculosis, is a chronic infection and one must attempt to maintain nutrition. Meat, fresh vegetables, milk, in fact any foodstuff prepared in a digestible manner is acceptable.

The anemia that develops so rapidly in patients with rheumatic fever is caused by the toxemia of the disease. The iron released from the destroyed red blood cells is stored in the liver and spleen and is available in sufficient quantity for hemoglobin formation when the infection has subsided. The administration of iron, therefore, during the stage of active infection is unnecessary, it will not combat the anemia and may serve to disturb the digestion. It may be given in small doses—10 grains of iron and ammonium citrate three times a day—during convalescence.

Heart stimulants are not indicated during the acute febrile period. The inflamed heart muscle seems to be refractory to such stimulants. Indeed it is often overirritable and the incautious administration of digitalis may quickly give rise to toxic symptoms, or to changes in rhythm such as auricular fibrillation. Digitalis should never be used during acute rheumatic carditis. Even when heart failure becomes severe during the stage of active infection, digitalis is ineffectual and recourse must be had to diuretics such as ammonium chloride 20 to 30 grains three times a day, with occasional injections of a mercurial diuretic such as mercupurin or salyrgan.

In view of the association of tonsillitis with rheumatic infection some have advocated tonsillectomy even during the febrile period in the hope of preventing further infection. This is a pernicious and dangerous practice which often leads to exacerbations of the systemic infection. Tonsillectomy, when indicated, must be performed after the infection has subsided.

In summary, it is evident that treatment of early and potential heart failure in acute rheumatic carditis consists in sparing the heart all unnecessary work, and in maintaining the body nutrition and presumably the resistance as best one can. There is no direct cardiac therapy.

#### FAILURE OF THE HYPERTROPHIC HEART

**Chronic Rheumatic Valvular Heart Disease** **Hypertensive Heart Disease**—In the absence of myocarditis and of advanced disease of the coronary arteries heart failure rarely occurs unless the heart muscle has been hypertrophic for some time. Hearts handicapped by chronic valvular deformities following rheumatic infection, or by high arterial pressure have the common feature of hypertrophy and dilatation, which slowly progresses. With the lapse of years dyspnea and palpitation herald the onset of myocardial weakness. It is not always easy, however, to be certain that these symptoms indicate heart failure. Young women with mitral stenosis often have neurocirculatory asthenia as well, and in them the

cardiorespiratory distress may be caused by the neurogenic disturbance, by loss of the regulatory balance of the cardiac and vasomotor nerves. Similarly women with hypertension often complain of hot flushes, vertigo, rapid palpitation, dyspnea, and sticking precordial pain, determined by a similar neurogenic disorder. In such patients the symptoms are out of all proportion in their intensity to the anatomical changes in the heart. Were they determined by heart failure one would find a large dilated heart, distended neck veins, cyanosis, and congestion of the lungs and liver. Instead, the heart is small and there is no venous congestion. Even in the presence of organic heart disease the diagnosis of heart failure does not follow automatically from the appearance of symptoms such as dyspnea and palpitation. The symptoms must be correlated with the heart lesion. In these patients with psychoneurotic disturbances manifesting themselves in a cardiovascular symptomatology, the erroneous diagnosis of heart failure, with the restrictions and treatment consequent upon it may do incalculable harm.

Certain objective criteria are of assistance in determining whether there is actual failure of the heart muscle. With early heart failure the pulse rate is usually rapid, and the acceleration persists during sleep—a rapid rate caused by neurogenic factors drops to normal during sleep<sup>1</sup>. The determination of the circulation time of the blood, which is very simple with the newer methods, is very helpful. A delayed circulation time indicates heart failure.

In the rheumatic group heart failure may at any time be induced by a fresh rheumatic infection. The treatment of such failure has been outlined in a previous section.

Another factor that commonly precipitates failure of a hypertrophic heart is bodily activity that overtaxes the reserve power of the heart. Such overexertion may produce an insidious cumulative effect so that the time comes when the patient discovers that he cannot carry on his ordinary activities without dyspnea and palpitation, and that he tires easily. This is the first indication that the heart is beginning to fail.

Since this failure is caused by persistent overtaking of the heart, treatment must first be directed to relieving the muscular pump of all unnecessary work. Nothing is as valuable as a few weeks' rest in bed, even though the patient is not acutely ill. In most instances bed rest need not be absolute, and bath room privileges may be allowed. After the period of bed rest the patient is kept in the house for another few weeks and is then very gradually allowed to resume his activities. But he must be alert to learn the limits to which he can go. The onset of dyspnea is usually the best indication that the particular activity is too great a burden on the heart. The tempo of activity is as important as the amount of work done. If the patient learns to move and to live at a leisurely pace, avoiding all hurry, he will be astonished to discover how much he can do. Stair climbing traditionally is a great bugaboo to the patient with heart disease. Stairs are not nearly as dangerous or harmful as we make our patients suppose. Many of these patients, after they have recovered from early heart failure, can climb stairs if they walk slowly, and if they rest on the way if necessary. It does them no harm.

The diet requires little comment. It should be liberal and varied. No particular foodstuffs, in my experience, are either helpful or harmful. I have seen no benefit from a high carbohydrate diet. Of course, foods known to disagree with the patient must be avoided. A rest period should follow every meal. The chief need is to prevent overloading the stomach and to keep the bulk of the meals low. If the patient is obese, dietary restrictions to induce loss in weight may be necessary. The fluid intake should not exceed a quart and a half in twenty-four hours.

Drugs. Digitalis is particularly helpful in early failure of a hypertrophic heart. Since there is no emergency, moderate dosage of  $1\frac{1}{2}$  grains of digitalis twice a day, given for several months, is adequate. Some have urged that these patients take small doses of digitalis for the rest of their lives, in the belief that in this manner the contractile power of the heart is permanently kept at a higher level. There is some question as

to the validity of this view, and in my experience such continuous dosage is rarely desirable in these cases

Aside from digitalis little medication is indicated. Mild sedatives such as phenobarbital, or a mixture containing from 5 to 10 grains of chloral hydrate and 10 grains of sodium bromide to the dose are often useful, particularly in patients with hypertension

There are some patients with hypertension or with insufficiency of the aortic valve and very large left ventricles in whom the premonitory symptoms of heart failure may be lacking or overlooked. In them the first sign of heart failure, and it is a sign of left ventricular failure, is an attack of nocturnal "asthma" or of paroxysmal dyspnea. This may or may not be associated with pulmonary edema. Paroxysmal dyspnea is a very complex phenomenon of which a most important component is a reflex irritation of many medullary centers. This gives the lead for the most efficacious treatment—namely the hypodermic administration of morphine. In such an attack full doses, as a rule  $\frac{1}{2}$  grain, of morphine sulphate must be given. This may be repeated if necessary. This usually brings speedy relief. Prevention of further attacks involves the administration of digitalis to strengthen the heart, and the control of fluid exchange. If such a patient has been receiving no digitalis he should take about 6 grains daily for two days, followed by 3 grains daily. Still more important is the reduction of fluid intake to below 1000 cc a day, with no fluids taken after 6 p. m. Diuretics should be given as well. Not infrequently aminophyllin is of considerable value. In the acute attack intravenous injection of an ampule containing 4 grains may give immediate relief. To prevent attacks aminophyllin is given in  $1\frac{1}{2}$  grain tablets of which one or two are taken three times a day.

In the more stubborn cases, however, all of these measures will be ineffectual in preventing the recurrence of attacks. Here the more powerful diuretics must be used. Ammonium chloride 30 grains three times a day is best administered in enteric coated tablets of  $7\frac{1}{2}$  grains each. With this a mercurial

diuretic should be given intramuscularly or intravenously. There are several available—mercupurin and salyrgan which can be given intramuscularly or intravenously, or neptal which is used only intramuscularly. The dosage of each is from 1 to 2 cc. This dose can be repeated every five to seven days depending on the indications, and can be continued for long periods of time. Care should be taken not to use these mercurial diuretics in patients with kidney insufficiency, that is, with a low specific gravity urine, with significant nitrogen retention, or with much albumin and red blood cells in their urine. In such cases they may cause further kidney damage and may even cause death from uremia. In the use of ammonium chloride too, it must be remembered that this drug acts by producing acidosis, and that at times overdosage produces too great a degree of acidosis, with rapid respirations and other toxic manifestations.

Heart failure may be induced for the first time by acute overexertion. In lesions which have resulted in preponderant left ventricular enlargement such failure manifests itself with a clinical picture resembling paroxysmal dyspnea, intense dyspnea with or without pulmonary congestion or edema. The treatment of this state has just been outlined. When failure involves chiefly the right ventricle, as in patients with mitral stenosis, the outstanding features in addition to pulmonary congestion are distention of the neck veins, engorgement of the liver and peripheral edema. It is in such cases of sudden right heart failure that phlebotomy is particularly useful. At least 500 cc should be withdrawn. Digitalis should be given in large doses so that about 25 grains are given in the first three days. If the patient's condition is really critical the first dose may be an intravenous one of 4 cc. Recovery is often hastened by the administration of ammonium chloride and a mercurial diuretic.

After recovery from the acute stage of sudden heart failure, the patient must still be restricted for some time to allow of the fullest possible restoration of cardiac reserve. He should be kept in bed one month, and another month or two should

elapse before he is allowed to resume his wonted activities Digitalis in doses of about  $1\frac{1}{2}$  grains twice a day should be given for the whole period

The sudden onset of auricular fibrillation is often the precipitating cause of heart failure It is the rapid rather than the irregular ventricular rate that is responsible for the circulatory insufficiency The intensity of the failure depends on additional handicaps occasioned by the degree of valvular deformity and of impairment of the myocardium Thus patients with Graves' disease whose hearts are anatomically normal are often little embarrassed by the onset of auricular fibrillation, while those with mitral stenosis or long-standing hypertension usually become very ill with congestive heart failure

In addition to the general methods of dealing with heart failure, which have been discussed, the immediate indication is to reduce the heart rate to its normal level This is readily accomplished by the administration of adequate amounts of digitalis The procedure is very simple, and need not be complicated by calculations of body weight dosage or of pulse deficits

**Digitalis in Auricular Fibrillation**—When the auricles are fibrillating the auriculoventricular node is bombarded by some 450 impulses of varying intensity every minute It can only respond to a certain number of these—usually to from 100 to 160 a minute These impulses then pass through the auriculoventricular conducting tissues to the ventricles and initiate ventricular contractions The ventricular rate varies from 100 to 160 a minute depending on the number of impulses that come through Digitalis depresses the function of the auriculoventricular conduction tissue, and so blocks the passage of the weaker impulses and prevents them from initiating ventricular contractions Thus the ventricular rate is slowed Within certain limits the degree of block, and therefore of ventricular slowing depends on the amount of digitalis administered There is no absolute measure of digitalis dosage, the amount of digitalis needed to slow the ventricles when the



auricles are fibrillating depends largely on the personal idiosyncrasy of the patient. There can be only one rule. Give enough digitalis to reduce the ventricular rate to about 70 and to maintain it at this level.

For most purposes the  $1\frac{1}{2}$ -grain, 1 cat unit, tablet of digitalis, of which there are many good preparations on the market, is the most satisfactory. Intravenous or intramuscular administration is indicated only in emergencies or when the patient cannot swallow.

The speed with which digitalization is carried out depends upon the severity of the patient's symptoms. If the ventricular rate is very rapid and the patient very ill, 4 cc. of an appropriate preparation may be given intravenously, followed immediately by 6 grains by mouth. It takes about six hours before digitalis given by mouth is absorbed and acts on the heart. Further dosage is determined by the response of the ventricular rate to the medication. As long as the heart rate counted at the apex remains above 100, fairly large doses can be safely administered. Thus the apex rate is counted every six hours and if it remains rapid 6 grains are given at each six-hour period. When the rate falls below 100, which will usually occur within twenty-four hours, the dosage is reduced at first to  $1\frac{1}{2}$  grains every four hours. As soon as the ventricular rate has dropped to between 70 and 80, one must determine the amount of digitalis necessary to maintain this rate. This is usually in the neighborhood of 3 grains a day, although some patients will require more and some less. The exact dosage must be determined by trial and error, by observing the ventricular rate. It is well to teach these patients how to count their ventricular rate so that they can learn to adjust their own digitalis dosage, for their need of digitalis may vary from time to time. If the heart is large and the apex beat forceful this can be done by palpation, otherwise the patient should learn to count the apex rate with a stethoscope.

If the indications for digitalization are not so urgent, the drug should be given more slowly. As a rule, the administration of  $1\frac{1}{2}$  grains every four to six hours will slow the ventricles in

a few days. Even in these cases the initial dose may be larger—6 grains. When the heart is slowed the maintenance dose must be worked out as indicated above. *In all cases digitalis must be continued indefinitely as long as the auricular fibrillation persists and the ventricular rate tends to increase as digitalis is withdrawn.* It is far too common to encounter patients with auricular fibrillation who, after having had compensation restored, again develop heart failure because they stopped taking digitalis.

A knowledge of the toxic effects of digitalis is, of course, necessary. Headache, nausea, vomiting, and the appearance of extrasystoles, particularly of bigeminal rhythm, are the common signs of digitalis poisoning. The development of any such signs or symptoms must lead to cautious evaluation of their significance, and to the temporary stoppage of digitalis administration. Nausea caused by congestion of the gastric mucosa and congestive distention of the liver commonly is associated with heart failure and calls for more vigorous digitalis therapy. As a rule, nausea experienced immediately after taking the medication is not due to digitalis. Digitalis nausea is very persistent and distressing.

**Quinidine in Auricular Fibrillation**—The restoration of normal sinus rhythm by means of quinidine is rarely indicated in patients with auricular fibrillation. The danger of embolism, or of sudden death from the toxic action of the drug, together with the great tendency of auricular fibrillation to recur make the use of quinidine of doubtful value in most cases. There are times, however, when the drug is invaluable. When the heart—particularly the auricles—is little enlarged, and when the absolute irregularity is, so to speak, an accidental occurrence rather than a sign of progressive heart failure, restoration to normal rhythm with the aid of quinidine may be of lasting value. Such cases are rare, except in association with hyperthyroidism. In hyperthyroidism, however, even if the heart is small there is no point in restoring normal rhythm as long as the hyperthyroid state persists for this will certainly lead to recurrence of auricular fibrillation. Subtotal thyroid

ectomy alone usually causes spontaneous return of normal rhythm within a few weeks after operation. If this does not occur within a month following the thyroidectomy quinidine should be given to abolish the irregularity.

When it has been determined that the case is suitable for quinidine therapy the drug should be administered in the following manner. The patient is kept in bed. First two test doses of 3 grains each of quinidine sulphate are administered two hours apart. If this gives rise to no untoward symptoms one may proceed. At first 3 grains of quinidine sulphate are given every two hours, day and night, until sinus rhythm returns or until symptoms of cinchonism such as tinnitus, nausea, or diarrhea, appear. If this does not lead to the desired result within two or three days the dose is doubled, *i e*, 6 grains of quinidine sulphate are given every two hours for twenty-four hours if necessary. If this does not arrest the fibrillation, 6 grains every hour for 10 doses may be tried. Quinidine is rapidly excreted and the effective concentration of the drug in the body seems to be the important element in its efficacy. If normal sinus rhythm has been restored the concentrated dosage should immediately be stopped and 3 grains of quinidine should be given every four hours for the first day, every five hours for the next few days, and then three times a day for a few weeks. Then the drug should be stopped completely.

In patients with paroxysmal auricular fibrillation in whom the attacks of irregular heart action are repeated at frequent intervals, quinidine may be given to prevent attacks. It is difficult to determine the optimum dosage, but as a rule 3 grains three to five times a day are efficacious. If it is known that attacks come at a particular time of day, or in relationship to a meal, dosage should be concentrated at this period.

**Paroxysmal tachycardia** may initiate heart failure. Short periods of tachycardia, of a few hours or less, rarely cause much discomfort even when the heart is already damaged. If the rapid rate persists, cardiac distress becomes manifest, and even serious failure may ensue. Attempts should first be

made to arrest the tachycardia by firm pressure on the carotid sinus which is situated at the bifurcation of the common carotid artery. If the maneuver is ineffectual on one side of the neck, it should be tried on the other. If these attempts fail, firm pressure on one of the eyeballs may restore normal rhythm. At times taking a deep breath, or bending forward or swallowing may bring the desired result. If these simple measures are unsuccessful recourse should be had to quinidine. It is administered as in auricular fibrillation. The drug may also be used similarly to prevent recurrent attacks of paroxysmal tachycardia. At times oral dosage with quinidine is ineffectual in arresting this abnormal rhythm and the persistence of the rapid heart rate may endanger life. Under such circumstance from 7 to 10 grains of quinine dihydrochloride, given intramuscularly, may promptly restore sinus rhythm. Still more dramatic, and almost instantaneous effects have been achieved by intravenous administration of quinine dihydrochloride. I do not recommend this last method for the drug is a highly toxic protoplasmic poison, and I have seen cardiac standstill as well as transient intraventricular block follow its intravenous use.

#### HEART FAILURE MANIFESTED BY ANGINAL PAIN

Patients with angina pectoris have heart failure as truly as do those with dyspnea and evidences of congestive failure. The presenting symptom here is purely subjective and may be unaccompanied by any objective manifestations of disease. Thus it becomes important to recognize anginal pain and to distinguish it from other less significant types of precordial pain. The pain of angina pectoris is usually experienced as a pressure or cramp beneath the sternum or in the III interspace to the left of the sternum, it may radiate to the neck, the left shoulder or the left arm, it is usually provoked by effort, excitement or a meal, it compels the patient to arrest all activity until the pain is gone, it is not associated with dyspnea or palpitation, it is relieved by nitroglycerin. When the "heart" pain is sticking or stabbing in character, when it is

localized near the apex, when it is more or less continuous and unrelated to exertion, when it is associated with palpitation one is dealing not with angina pectoris due to coronary artery disease, but with a nonspecific pain usually associated with functional cardiovascular disorders and with an anxiety neurosis

The ease with which anginal attacks are provoked gives a measure of the severity of the lesion of the coronary arteries, and of the degree of heart failure. Progress of the disease is indicated by increased frequency of attacks, of attacks provoked by lesser and lesser activity, and by the appearance of attacks when the patient is at rest, particularly during the night. In the present state of knowledge we cannot hope to arrest the progress of the arterial disease by treatment, but we can greatly reduce the frequency of attacks, and often lessen the tendency to coronary thrombosis.

Coronary thrombosis, of course, is the complication most to be feared in these patients. While all too often this dreaded catastrophe occurs without known provoking cause, often even unheralded by previous anginal seizures, not infrequently its occurrence may be traced to a definite exciting cause.<sup>3</sup> A silk weaver underwent a sudden severe strain as he caught a heavy falling weight on his loom. Immediately he experienced a tearing pain under the sternum and quickly developed classical signs of coronary thrombosis. A cutter of cloth lifted a double bolt of silk in the belief that it was a single one. With this he felt a sharp pain to the left of the sternum which soon subsided. An hour later, while walking out of the building, he experienced his first attack of angina pectoris. A doctor ran up several flights of stairs to see a sick patient. On arriving at the top he developed intense substernal pain which persisted and was followed by classical signs of coronary thrombosis. These examples indicate how, in a patient with coronary artery disease, an unusual effort may be followed by coronary artery occlusion. They give a most valuable clue to the proper treatment of these patients.

The most important measure in the handling of patients

with angina pectoris is regulation of their lives. They must learn that an attack of pain is a warning that they have overstrained the heart. They must school themselves to live a leisurely life without hurry and without high emotional pressure. In particular they must avoid spurts of exertion such as running to catch a bus, or straining to lift a heavy object. If they learn to move slowly they will often be agreeably surprised at what they can do without inducing pain. It is particularly important to avoid all exertion for about an hour after eating.

Whether or not they can continue working depends upon their occupation, and on whether their work induces anginal seizures. Of course, a ditch digger cannot continue at his work, but many factory workers can carry on without apparent harm to themselves. It is striking that most such workers experience no distress while working, but have their greatest difficulty in traveling to and from their place of employment. Whenever possible a man should be allowed to continue to work. There is no convincing evidence that most occupations act unfavorably on these patients or that they predispose to coronary occlusion. If the factor of acute strain, and of post-prandial exertion can be eliminated, work does no harm to their hearts, and prevents them from becoming hopeless, despondent cardiac invalids. In all such cases, however, the physician must protect himself by explaining to some member of the family that although the work will do no harm, the nature of coronary disease is such that a serious attack can come at any time. It may happen tomorrow or not for years. If the patient cooperates reasonably he will not injure himself by moderate activity for an attack may come as readily when he is resting quietly.

The diet needs little elaboration. The patient may partake of anything that agrees with him. The only precaution that he must take is to eat temperately to avoid overfilling his stomach. Better to arise from the table a little hungry and if necessary eat again in a few hours, than overdistend the stomach. It is also advisable to lie down or to rest in an easy

chair for three quarters of an hour to an hour after every meal

Smoking, too, is a matter about which there are many opinions but few facts. In spite of recent work suggesting tobacco allergy in certain young individuals with arterial disease, the significance of the findings is not clear. If it is true that tobacco sensitization is responsible for coronary artery disease, one cigarette would be as bad in its effect as many. The fact remains that the relationship is not yet proved, and that many nonsmokers have coronary disease, and many individuals with coronary disease can smoke with seeming impunity. Some individuals, it is true, but they form a small minority, develop anginal pains after smoking, and for these tobacco must be absolutely prohibited. Most patients with angina pectoris experience no apparent ill effects from tobacco, and they may be allowed to smoke in moderation.

Alcohol should never be taken in excess, nor in sufficient quantity to produce exhilaration, but an occasional glass of wine or a small amount of whisky is often soothing and beneficial when the patient is tired or irritable. This holds particularly for older people.

The most important drug is nitroglycerin. Neither nitroglycerin nor other nitrites are of any value taken regularly with a view to preventing attacks. Their only value lies in relieving the attack itself. Every patient with angina pectoris should carry  $\frac{1}{100}$ -grain tablets of nitroglycerin with him, and in case he is incautious or unfortunate enough to have an attack he should place one under his tongue and let it dissolve there. This may be repeated in a few minutes if no relief is obtained.

Of other drugs sedatives are of the greatest value. Phenobarbital  $\frac{1}{2}$  grain three times a day is one of the best. In patients with high blood pressure a chloral and bromide mixture containing about 7 grains of chloral and 10 grains of sodium bromide to the dose is most useful. Often the patient complains of flatulence. In such cases a carminative is helpful. The bowels must be regulated and straining at stool must be avoided.

The use of many drugs has been advocated to dilate the coronary arteries and to improve the blood flow through the myocardium. Most of these are purine derivatives. The most popular of them all, and those for the use of which there is some experimental evidence, are theobromine sodium salicylate, of which 5 to 15 grains are given three times daily, and aminophyllin which is administered in  $1\frac{1}{2}$ -grain tablets of which one or two are taken three times a day. In spite of optimistic reports of several observers I have been unable to convince myself of their value. They are harmless, however, although at times they do upset the stomach, and may be given when it is necessary to give the patient something. The same holds true for the various muscle and organ extracts which are given with the similar hope that they may dilate the coronary arteries. These, too, I have found uniformly ineffectual.

The very best treatment of all, when everything else fails, is to keep the patient at absolute rest in bed for a month. This will often not alone prevent attacks for the period of rest, but increase the cardiac reserve to such an extent that the patient may be able to be quite active without symptoms for some time afterward. Sympathectomy is never indicated, but in very stubborn cases paravertebral alcohol block, if carried out by an expert, may relieve the patient from further attacks of pain. Often the anginal pain is replaced by a severe neuralgic pain at the site of the injection, which is worse than the pain it was sought to cure. Finally, when everything else has failed, one must consider the desirability of total ablation of the thyroid gland. This seems to be of real value in selected cases.

I shall not at this time discuss the treatment of coronary thrombosis, for when this occurs one can no longer speak of early heart failure. But one point must be emphasized. When a patient has recovered from such a cardiac infarction, and when, as happens so often, he has no signs or symptoms of congestive heart failure, and when his anginal seizures are not too readily provoked, he should be handled like the patient with simple angina. In particular nothing will be gained by making



him a permanent invalid. He should be kept under observation, but should be encouraged cautiously to resume his former occupation if it is at all feasible.

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THE HEART IN RHEUMATIC FEVER AND ACUTE RHEU-  
MATOID (INFECTIOUS) ARTHRITIS

A PRELIMINARY report of a means of making a differential diagnosis between rheumatic fever and acute rheumatoid (infectious) arthritis in adults was recently made by us<sup>1</sup> In 17 patients with acute rheumatoid (infectious) arthritis no definite evidence of myocardial involvement was recorded while in 63 cases of rheumatic fever definite evidence of this complication appeared in 100 per cent of the cases The discovery of the presence or absence of cardiac damage appeared to be so clear cut a means of dividing nonspecific acute polyarthritis in adults into two groups that the preliminary work was extended further to include 50 cases of acute rheumatoid (infectious) arthritis This group was compared electrocardiographically with the 63 cases of rheumatic fever and clinically with the last 50 of those in which an acute polyarthritis was present.

The similarity of acute rheumatoid (infectious) arthritis and rheumatic fever from both the clinical and laboratory viewpoint was commented upon and reviewed in our earlier report.<sup>2</sup> To appreciate the difficulty of diagnosis two case histories will be cited

Case I—An Italian, thirty years of age, was admitted to the Mount Sinai Hospital, January 15, 1931, and discharged February 3, 1931, with the diagnosis of acute rheumatoid

(infectious) arthritis Sixteen years previous he had been sick for three months with a similar acute polyarthritis The present illness began six weeks before admission with an upper respiratory infection and pain in the lumbosacral region which forced the patient to go to bed Four days later the right knee became painful, red, hot and swollen Inflammation in this joint subsided in three days but migrated successively to wrists, shoulders and left knee There had been persistent mild fever, with chilliness, and during the six weeks he had lost 25 pounds in weight Physical examination revealed a robust young man, in pain, with right wrist and both shoulders inflamed The teeth were in poor condition, the tonsils were large, the faucial pillars were hyperemic A faint systolic murmur was heard at the apex The hemoglobin was 70 per cent, the white blood cells 12,800, the polymorphonuclears 58 per cent, lymphocytes 38 per cent, monocytes 4 per cent The blood culture, urine examinations and gonorrheal complement fixation test were negative The temperature reached 104° F on the fourth day and then gradually returned to normal on the sixth The pain was not relieved by salicylate therapy A tonsillectomy was performed on the sixth day with almost immediate improvement The patient was discharged eighteen days after admission, quite able to go to work The electrocardiogram taken daily showed no abnormality other than a sinus arrhythmia

Clinically, the case resembled rheumatic fever in all respects but three There was no electrocardiographic or clinical evidence of myocardial involvement The pain was not relieved by salicylates and, finally, the removal of a focus of infection (the tonsils), immediately preceded improvement

**Case II**—An Austrian, forty years of age, was admitted April 11, 1933, and discharged May 14, 1933 For six years this patient had been ill with joint pains on an average of once a year The present experience began with a "grippe" four weeks previous, that is, he suffered with pain all over his body After a week in bed the pain became localized in both ankles,

knees, toes, fingers and wrists. Fever and sweats occurred. On physical examination, the patient was found to be obese and his pharynx was congested. The heart was entirely negative although a faint apical systolic murmur was present. The left knee was slightly enlarged, tender, and a patellar click was obtained. The right knee joint and the wrists were also tender. Over the right olecranon a nodule was felt. The hemoglobin was 88 per cent, the red blood cells 4,540,000, the white blood cells 20,400, the polymorphonuclears 87 per cent and lymphocytes 13 per cent. The sedimentation time was fifteen minutes. During the first week, the temperature ranged from 101° to 103.6° F, pulse rate 78 to 100 beats per minute. The patient received salicylates, pyramidon and iron throughout hospitalization. The sedimentation rate increased to eleven minutes and recourse was had to intravenous injection of typhoid bacilli, beginning April 29, 1933. From the inception of this mode of therapy the patient improved. The olecranon nodule was excised and reported by Dr. Paul Klemperer as suggestive of a rheumatic nodule.

This patient, too, presented no clinical or electrocardiographic evidence of myocardial involvement and for this reason his malady was diagnosed as rheumatoid (infectious) arthritis. A history of similar attacks over a period of six years with no resulting cardiac involvement lends further support to this diagnosis, as does, also, the prompt response to typhoid injection. That the nodule over the olecranon was indistinguishable pathologically from that seen in acute rheumatic fever bears out a trite observation, namely, that the subcutaneous nodule is found in both diseases and is alike morphologically.<sup>3</sup>

Altogether fifty cases of acute rheumatoid (infectious) arthritis were studied clinically and electrocardiographically. These were compared with 63 cases of acute rheumatic fever. As far as possible daily electrical tracings were taken which were always recorded while the patient was in bed. Digitalis was never dispensed but salicylates and pyramidon were used throughout the course of the disease.

Since the electrocardiogram is an objective means of study, our observations in this field will first be reported (Table 1)

TABLE 1  
ELECTROCARDIOGRAPHIC FINDINGS

Number of patients	Rheumatoid (infectious) arthritis	Acute rheumatic fever
	50	63
Definite electrocardiographic evidence of myocardial involvement	Per cent. 0	Per cent 100
<i>Changes in Rhythm</i>		
Bradycardia	20	20 8
Tachycardia	34	68 3
Sinus arrhythmia	14	22 4
Sino-auricular block	0	9 6
Auricular premature beats	0	9 6
Ventricular premature beats	0	4 8
Nodal rhythm	2	1 6
Nodal tachycardia	0	1 6
Interference sinus and auriculoventricular nodes	0	3 2
Auricular fibrillation	0	3 2
Auricular flutter	0	3 2
<i>Changes in Electrocardiographic Waves</i>		
P-R (0.2 second)	14	12 8
P-R (over 0.2 second)*	10	52 8
Dropped beats	0	4 8
RST changes	0	84 8
T-wave inversions	0	40 0
Iso-electric (flat) T-waves	10	28 6
Inversion T <sub>2</sub> only (transient)	8	8 0
Transient QRS abnormalities	0	6 4
Change voltage QRS	2	14 3
Transient large Q <sub>2</sub>	0	9 6
Transient L A. D	0	11 2
Transient R A. D	0	3 2
P wave changes	2	12 8

\* Four cases 0.21 second, one 0.22 second, none more than 0.22 second

The outstanding feature is the lack of electrocardiographic evidence of myocardial damage in the patients suffering from acute rheumatoid (infectious) arthritis and its 100 per cent presence in rheumatic fever patients. Among the former group,

there was not a single instance of auricular fibrillation, auricular flutter, prolongation of the auriculoventricular conduction time (P-R interval) beyond 0.22 second, partial heart block with dropped beats, RS T changes, T wave inversions or development of large Q waves in leads III. Many minor changes, even, were absent, such as sino-auricular block, auricular or ventricular premature beats, nodal tachycardia or interference of sinus and nodal rhythms. The electrocardiographic abnormalities observed were slight. There were five cases in which the auriculoventricular conduction time was prolonged beyond 0.2 second. In one of these five cases the P-R interval attained 0.22 second, in the remaining four the maximum defect was 0.21 second. These figures are not far from the accepted upper limit of normal, namely, 0.2 second. Another way of emphasizing that there was meager electrocardiographic evidence of myocardial damage is to contrast the results of these electrocardiograms with those obtained in the 63 cases of acute rheumatic fever where every single case showed unequivocal signs of severe myocardial involvement (Table 1).

The practitioner of medicine is primarily interested in learning wherein rheumatic fever and acute rheumatoid (infectious) arthritis differ clinically. The study revealed what the electrocardiogram has already shown. In rheumatoid (infectious) arthritis there is no clinical evidence of endocardial, myocardial or pericardial disease. Throughout the entire illness, and this lasted as long as one hundred and eight days in one instance, there was no development of a single systolic murmur which might be considered organic in character, no development of a diastolic murmur, no pericarditis, no thrill, no evidence of myocardial enlargement, no auricular fibrillation or flutter, no tachycardia of more than 120 beats per minute, no heart block. In fact, the outstanding feature was the absence of even minor clinical evidence of toxic effect on the heart muscle, such as auricular or ventricular premature beats (extrasystoles). In any infectious disease of long standing, with fever and prostration of the patient, one not uncommonly

observes minor cardiac irregularities such as auricular and ventricular premature beats. In the acute rheumatoid (infectious) arthritis group these were not once observed. Hence, the absence of clinical signs of organic heart disease in patients with acute polyarthritis is very good evidence that the patient has acute rheumatoid (infectious) arthritis and not rheumatic fever. Only 30 of the 50 patients with rheumatic fever presented signs of organic cardiac disease on admission, but 15 more developed signs during the course of the illness, leaving 5 patients with rheumatic fever who gave no sign of heart involvement clinically, although the electrocardiograms were definitely abnormal. Clinically, therefore, it may be difficult to distinguish the two conditions but in the presence of definite clinical evidence of heart disease the diagnosis is rheumatic fever.

The onset with upper respiratory infection, with or without epistaxis, the fever, the migratory type of joint involvement, the tenderness, swelling and redness of the joints, the sweating, the prostration, the leukocytosis, the secondary anemia, the rapid sedimentation time, the subcutaneous nodules, all were found in both rheumatic fever and rheumatoid (infectious) arthritis. However, aside from the presence or absence of cardiac involvement it will be noticed that there were some definite clinical differences. The acute rheumatoid (infectious) arthritis patient was inclined to be slightly older (Table 2). The average age was thirty-six, the youngest, eighteen and the oldest sixty-six. This compared with an average age of twenty-six in the rheumatic fever group, the youngest being thirteen and the oldest fifty-five. Epistaxis as an onset, appeared less common in the patients with arthritis. In this group it occurred twice, whereas, in the rheumatic fever series it was present ten times. A history of previous attacks was more frequent in rheumatic fever and the pulse rate and temperature attained higher levels. No distinction in the joints involved was noted except in the sternoclavicular. In the rheumatic fever patients it was involved six times, and only once in the rheumatoid arthritis. Another difference was that

TABLE 2

## SUMMARY OF ONE HUNDRED CASES OF ACUTE POLYARTHRITIS

	Rheumatoid (Infectious) arthritis	Acute rheumatic fever
Number of patients	50	50
Average age	36	26
Youngest	18	13
Oldest	66	55
Males	28	32
Females	22	18
Average hospital stay	38 days	44 days
Clinical evidence of organic heart disease	0	45
Onset		
Acutely	35	43
Subacutely	14	7
Upper respiratory infections	20	33
Epistaxis	2	10
Previous attacks	13	22
Pulse		
More than 110 beats per minute	5	19
More than 120 beats per minute	1	4
Temperature		
104 °F	3	13
105 °F	0	3
Monocyclic type of temperature	40	42
Polycyclic type of temperature	10	8
Joint deformities	10	0
Sternoclavicular involvement	1	6
Foci of infection		
Teeth	15	10
Tonsils	20	13
Sinuses	14	7
Response to typhoid injection		
Improved	4	
Unimproved	1	2
Response to tonsillectomy		
Improved	3	

clinically and according to roentgen ray film there were evidences of permanent changes in the joints of ten patients with acute rheumatoid (infectious) arthritis, whereas, in the cases of rheumatic fever slight indefinite changes were reported but once despite the fact that in the latter disease recurrent attacks were more common



The blood count including hemoglobin, white blood cell count and differential were alike in both diseases. Similarly, the sedimentation time was equally rapid. Slightly more foci of infection were reported in the acute rheumatoid (infectious) arthritis cases. In patients of this group, prompt disappearance of symptoms directly following tonsillectomy was noticed three times, improvement on intravenous injection of typhoid bacilli, four times, and no change, once. In rheumatic fever, injection of intravenous typhoid bacilli produced no improvement on the two occasions when it was employed.

### DISCUSSION

The investigation may suggest the criticism that the presence or absence of abnormal electrocardiograms may have influenced the clinicians in making the diagnosis. Since the publication of our preliminary report, there has been a tendency to do this. The importance of our observations is not diminished by this inclination. There appear to be two distinct types of nonspecific acute polyarthritis, one in which the heart is always and essentially involved, which we may call rheumatic fever, and one in which the heart is not involved, which we may name acute rheumatoid (infectious) arthritis. Moreover, the clinical and the electrocardiographic evidence of heart disease have practically always coincided. We are of the opinion that if the patient were carefully examined daily throughout the entire period of illness, clinical evidence of cardiac involvement would correspond to electrocardiographic, perhaps to even a greater degree than in our series, perhaps even to 100 per cent.

A definite involvement of the heart is essential for the diagnosis of rheumatic fever. There has been, in fact, a steadily growing opinion<sup>4</sup> that the presence of arthritis is unnecessary for the diagnosis of rheumatic fever. The important fact is that no diagnosis of rheumatic fever should be made unless cardiac damage is present clinically or electrocardiographically and in this investigation this fact has been used to distinguish acute rheumatic fever from a similar condition in

which no heart damage is apparent, that is, acute rheumatoid (infectious) arthritis

The question whether rheumatic fever and acute rheumatoid (infectious) arthritis sometimes occur in the same patient is an important one, for the answer might disclose how closely these diseases are allied. Although we have carefully searched for such a combination in our series of adults, we have found none. The patients whom we have designated as having acute rheumatoid (infectious) arthritis never revealed any evidence of acute heart disease during their illness, nor in a four year follow up study. Two patients with acute rheumatoid (infectious) arthritis had an essential hypertension, one with a systolic murmur at the apex. Their numerous electrocardiograms never gave any evidence of active myocardial involvement. The rheumatic fever group was constantly examined for the presence of a permanent arthritis and in no case in our series was this discovered. Our follow up period has not been long enough to be conclusive.

Many reports<sup>5</sup> have appeared in the literature giving details as to the presence of valvular disease in chronic arthritis. It is to be remembered that in this study we have not dealt with any chronic disease, either chronic valvular disease as such, or any chronic rheumatism or arthritis but rather we have studied two acute diseases, namely, rheumatic fever and acute rheumatoid (infectious) arthritis. Some authors<sup>5</sup> have reported the presence of chronic valvular disease in "rheumatoid arthritis," others<sup>6</sup> emphasized the rarity of the combination, but it is not clear what was meant by the term "rheumatoid arthritis." In fact, it was evident that some form of chronic arthritis was actually under consideration. Whether or not the presence of valvular disease in chronic arthritis is merely a coincidence is a problem outside the scope of this paper and we believe that a discussion of this subject would not clarify the present study. We shall continue to watch our cases.

In this paper, acute polyarthritis in adults only is considered, and we have no information in regard to a similar study in children. Still's disease is usually considered the

counterpart of rheumatoid arthritis in children. In this disease, pericarditis is not infrequent. There has never been a definite proof that this corresponded to rheumatoid (infectious) arthritis as we have studied it.

#### SUMMARY

Nonspecific acute polyarthritis in adults may be divided into two groups, one which presents definite involvement of the heart, either clinically or electrocardiographically, and the other which presents no definite evidence of cardiac involvement. The former is called rheumatic fever and the latter acute rheumatoid (infectious) arthritis.

In rheumatic fever, clinically, there are usually found during the course of the disease development of organic systolic murmurs and of diastolic murmurs, a pericardial rub, evidence of pericardial effusion, premature beats, auricular fibrillation or flutter, and partial heart block. The electrocardiogram depicts myocardial involvement in 100 per cent of the patients.

In acute rheumatoid (infectious) arthritis there is no evidence, clinically, of endocardial, myocardial, or pericardial involvement and neither does the electrocardiograph depict definite evidence.

It is suggested that careful daily clinical examination of the patient's heart may be sufficient for the differential diagnosis without the aid of the electrocardiograph. However, the electrocardiograph is, par excellence, the objective method for distinguishing the two conditions.

An onset with epistaxis and, during the disease, an involvement of the sternoclavicular joints are more commonly found in rheumatic fever. The patient suffering from acute rheumatoid (infectious) arthritis may improve dramatically or removal of a focus of infection such as diseased tonsils. Evidence of joint involvement clinically or by roentgen-ray film speaks for the presence of acute rheumatoid (infectious) arthritis.

No evidence was found either to prove that rheumatic fever

and acute rheumatoid (infectious) arthritis are related or that they may occur in the same adult patient

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#### THE DIAGNOSIS AND TREATMENT OF MENSTRUAL DISORDERS

ANY rational treatment must be based on knowledge of the underlying organic or functional pathologic changes as well as upon an accurate diagnosis. In dealing with menstrual disturbances, they in the main, fall into two broad classes, comprising decrease or abolition of the menstrual cyclical function, and the opposite, increase of bleeding, showing itself either by increased amount, increased frequency, or a combination of the two.

#### CLASSIFICATION

The disturbances of menstruation result either from organic, almost always local changes, or from functional disturbances, the majority of which are based upon endocrine disturbances.

**Organic Causes—Local Causes of "Amenorrhea"**—Amenorrhea and oligomenorrhea due to organic disturbances are unusual. They may be due to the absence of the vagina and a solid uterus. They may follow stenosis of the cervix or any portion of the vaginal canal, producing an apparent amenorrhea which is in reality, however, a damming back of the menstrual blood. Congenital atresias are the most frequent. Occasionally, an acquired stenosis due to operation, inflammation, thermocauterization or chemocauterization may produce these. Complete destruction of the menstruating endometrium by curettage or by atmocauterization has occasionally been reported.

**General Causes of Amenorrhea**—Amenorrhea due to pulmonary tuberculosis, change of climate, malnutrition or exces-

sive anemia are not infrequent. If the physician focuses his attention too strictly to the genital sphere, he will be misled.

*Local Causes of Menorrhagia and Metrorrhagia*—An increase of the amount of the menstrual blood lost (menorrhagia) as well as an increase of frequency of menstruation (metrorrhagia) is a common sequel to pelvic inflammation, especially gonorrheal. Many puzzling disturbances are found as direct sequels of abortion and pregnancy. These include irregular bleedings due to threatened and incomplete abortions, as well as their sequelae, ectopic gestation, and more rarely to incomplete involution after normal labor.

Tumors of the ovary, such as cancer, may cause excessive uterine bleeding. By far the most frequent causes of menorrhagia and metrorrhagia are uterine myomata.

Irregular bleeding from the genital tract may be due to erosion and eversion of the cervix as well as the bleeding from malignant tumors such as corporeal and cervical carcinomata, chorionepithelioma or any ulceration of the genital tract. Depending upon the site, the bleeding may show relation to menstruation (corporeal carcinoma) or be entirely unrelated to the cycle (vaginal cancer).

*General Causes of Menorrhagia and Metrorrhagia*—In polycythemia and purpura excessive bleeding may occur.

**Functional Disturbances**—Functional disturbances of the menstrual cycle are even more common than the organic. Our hormonal studies of the blood and urine<sup>1</sup> have shown that *ovarian underfunction* manifests itself as oligomenorrhea, amenorrhea, both primary (i. e., the failure of the establishment of menstrual function long after the time of puberty), and secondary. Dysmenorrhea, as well as sterility, even though the menstruation appears regularly, likewise fall into this group. In a large majority of instances, the endocrine disturbance is not limited to the ovaries but is primarily pituitary in origin, in spite of the fact that the most obvious symptoms may be noted in the thyroid gland, for example, and menstruation be affected only secondarily.

*Overfunction*, we have found,<sup>2</sup> includes premature sexual

maturity (pubertas praecox), puberty bleeding, the menorrhagias and metrorrhagias of adult life, preclimacteric bleeding, postmenopausal bleeding, and so-called "premenstrual tension" (in which no excess of bleeding is noted)

### DIAGNOSIS

The diagnosis of menstrual disturbances may require more knowledge and training than the average general practitioner can well be expected to acquire. On the other hand, if he exercises due care and routinely submits the patient to a thorough and complete examination, many gross errors can be eliminated. For example, he will not subject a patient to numerous and long-continued injections of so-called "endocrine remedies" because of amenorrhea, if he notes a median scar in the lower abdomen and on inquiry finds that a supravaginal hysterectomy has been performed, which thus explains the amenorrhea. Such an instance actually occurred recently in my practice.<sup>3</sup>

In order to make a correct diagnosis, it is necessary to examine each patient from head to foot, to take cognizance of marked deviations from the normal, especially of the secondary sex characters (feminine larynx, hair distribution, breast development, width of the hips, general build, etc.) I consider it an inexcusable omission when trying to determine the cause of menstrual disturbances, not to make a pelvic examination. In the adolescent or unmarried, a rectal examination is satisfactory and gives more information than the painful and disturbing vaginal examination through an intact hymen. Failure to make a pelvic examination in the married adult is even less excusable.

After a thorough general physical examination, which should include determination of hemoglobin content, the blood pressure, the status of the heart and lungs as well as a thorough external examination of the abdomen, pelvic examination is indicated. After inspection of the size and appearance of the clitoris, labia, introitus and hymen, the presence or absence of urethral and bartholinian discharge are looked for. Then either



by rectal or vaginal examination the size and shape of the cervix, the size and position of the fundus, as well as enlargement or abnormality of the tubes and ovaries should be determined. Deviation in the proportion between cervix and fundus, which in the normal adult is 1:3, frequently is of significance. Excessive length of the cervical segment with very short fundus is a sign of infantilism. When indicated, always in married patients, less often in the unmarried with intact hymen, the cervix should be visualized. In the child, adolescent, and unmarried, this can be done readily and painlessly by means of an endoscope introduced through the hymen. The sizes to be used vary between No. 10 to No. 14. Where the hymen offers no obstruction, an ordinary vaginal speculum may be used. Not infrequently, the source of irregular spotting or even bleeding can thus be determined at a glance (erosion, polyp, carcinoma).

In order to gain information from pelvic examinations, a certain amount of training and experience is, of course, essential. The size and position of the various pelvic organs vary within fairly large limits, particularly the size of the fundus, which is one fourth smaller immediately after menstruation, than just before the menstrual flow begins. Similarly, one or both ovaries may alter in size, depending whether a corpus luteum or a number of growing follicles have developed, such variations (100 per cent) being still within normal limits. Furthermore, the uterus of a multipara is almost always larger by one third than that of a nullipara of similar age, unless the patient is nursing, at which time a distinct, usually transient, so-called "lactation atrophy" may greatly reduce the size of the fundus. In at least 50 per cent of all nursing women lactation amenorrhea is noted and is physiologic.

**Amenorrhea.**—Confronted by a case of amenorrhea the logical sequence of the physician must be to first search for physiologic causes—pregnancy (even though the hymen be intact) and menopause, antecedent operations—hysterectomy, double oophorectomy, trachelorrhaphy (stenosis), excessive

curettage, general systemic disease—tuberculosis, grave anemia

Next, endocrine disturbance—thyrotoxicoses of long standing, reduced thyroid function with or without myxedema (basal metabolism minus 20 per cent to minus 35 per cent), marked obesity (a very frequent cause), extreme undernutrition or asthenia (also Addison's disease)

More rarely silent pituitary disease (sellar x ray, adrenal tumor, masculinizing tumor of the ovary (arrhenoblastoma<sup>4</sup>) cause amenorrhea.

**Menorrhagia and Metrorrhagia**—Confronted by a case of *bleeding from the vagina*, the probabilities will vary considerably according to the age of the patient

*Before the age of puberty*, local causes predominate—gonorrhea, urethral prolapse, injury from fall, masturbation or rape, cervical sarcoma, and very rarely premature puberty which may be functional, or due to ovarian tumor or pineal growth

*In the adolescent*, after the onset of menstruation, functional, so-called "puberty bleeding" is the chief cause. Abortal bleeding is occasionally encountered

*In the adult*, whether married or unmarried, the first investigation must be directed toward excluding pregnancy by examination of breasts, nipples, areola, colostrum. Threatened or incomplete abortion, ectopic gestation, postabortive or postpartum subinvolution (retained placental fragments) must be ruled out. In obscure cases the Aschheim Zondek or Friedman pregnancy tests prove invaluable

Of all the local conditions unassociated with pregnancy which cause excessive bleeding, fibroids of the uterus are the most common. Both menorrhagia and metrorrhagia may result. Intramural and subperitoneal fibroids less often produce metrorrhagia than the submucous variety

Excessive as well as irregular bleeding results from gonorrheal and septic tubal disease, both in the acute, chronic and subacute stages. The local findings vary from the "frozen

pelvis" to residual asymptomatic, slightly enlarged, cystic, adherent adnexa

Ovarian tumors may be associated with normal menstruation, amenorrhea or menorrhagia. Distinctive are the rare growths producing premature puberty and postclimacteric bleeding.

Carcinoma of the uterine fundus usually causes metrorrhagia. It may occur in combination with fibroids (2 per cent). Cervical cancer more often causes metrorrhagia or rather quite irregular bleeding, rarely menorrhagia.

Cervical erosions and eversions exceptionally produce severe bleeding, spotting is more usual.

Occasionally adenomyosis of the uterus, ovaries and parametria is encountered with or without "chocolate cysts," as the cause of excessive and irregular bleeding.

*After the menopause* 50 per cent of all uterine bleeding is due to corpus or cervix carcinoma. The nonmalignant causes are cervical polypi, submucous necrotic fibroids, cervical erosions.

*Only after all the above causes have been excluded is it justifiable to diagnose abnormal bleeding of functional origin.*

The strictly functional bleedings, both menorrhagia and metrorrhagia, are due to endocrine ovarian disturbance, but we are forced to conclude that the pituitary or the pituitary-thyroid sequence is the primary or active agent. In the vast majority of instances no overt pituitary symptoms ever become manifest.\*

Regularly at the onset of pituitary adenoma or carcinoma, at the onset of thyroid toxicoses and adrenal tumor, menorrhagia is noted. In the further course of these diseases amenorrhea supervenes.

*The average case of functional bleeding, irrespective of whether it is adolescent (puberty), adult or preclimacteric,*

\*Premature puberty can be produced in rodents by pituitary extracts. Experimental removal of the pituitary permanently abolishes the cycle. In de-pituitarized rodents the cycle may be temporarily reproduced by substitution therapy.

begins by excessive menstruation. Eventually, the bleeding may become continuous and all periodicity is lost. Secondary anemia with pallor, weakness, tiredness, dizzy spells, palpitation and edema supervene. I have encountered hemoglobin readings as low as 15 to 30 per cent.

In the early stages the uterus is usually soft, boggy, slightly enlarged. The ovaries commonly are normal, sometimes enlarged and polycystic (size of a small plum). At a later stage the uterus, remaining enlarged and symmetrical, becomes hard and fibrous.

Almost always curettings from these cases are voluminous, glistening, edematous—microscopically they show chronic hyperplasia, often of the cystic (Swiss cheese) variety.

From what has preceded it follows that the causal diagnosis of both amenorrhea and menorrhagia and metrorrhagia are involved and difficult. In not a few instances the actual causation cannot be determined by the most expert. The etiologic factors are numerous and varied. It need not surprise us that many methods of treatment have been tried and discarded. Whatever treatments are employed, they should have at least three qualities to recommend them—a sound theoretical basis for their use, harmlessness, the least radical possible.

#### TREATMENT

*Sterility* can only be regarded as an accessory to menstrual disturbances, appearing most frequently, when on an endocrine basis, in the underfunctional group. Its treatment requires no mention in this connection.<sup>5</sup>

**Dysmenorrhea**—Dysmenorrhea has not been dealt with under pathology or diagnosis because its pathology is unknown and its diagnosis offers no difficulty.

The most one is justified in saying about the etiology of dysmenorrhea is that in a majority of instances it is found in constitutionally infantile and neuter individuals. It is noted particularly in the groups of young women hard pressed by economic circumstances, who have not had a fair chance during their later school years and early working years. However, its

occasional occurrence in the economically most favored group, as well as in individuals who are fully normal in general constitution and in pelvic development, robs these observations of much of their value

In the last thirty years many hypotheses have been advanced for the cause of dysmenorrhea and have greatly influenced the treatment. Included are stenosis of the cervix, infantilism of the uterus, accompanied by poor muscular development, autonomic nerve imbalance, circulatory disturbances, painful or incomplete ovulation, etc. Based on such hypotheses, treatment by means of discission (dilatation and curettage, Dudley and Pozzi trachelorrhaphy, insertion of stem pessaries) has been used. Resection of the nerves of the broad ligament was practiced by Harris. Local anesthesia and cauterization of the so-called "nasal spots" was advocated by Fliess and others. Blair Bell opened the anterior fornix and "straightened out" the anteflexion. While these various forms of therapy "cured" a limited number and relieved others temporarily, none of the methods has stood the test of time.

In my own experience, the milder cases can be greatly helped by giving antipyretics combined with small doses of codeine, with the very onset of the pain. Usually a capsule containing acetanilid and phenacetin, each 3 grains and codem  $\frac{1}{4}$  grain may be taken three or four times a day. If sufficient relief is not afforded, atropine by mouth in a dose of  $\frac{1}{150}$  to  $\frac{1}{100}$  grain, to the point causing dryness of the throat, is given at the same time as the antipyretics. But the patient must be cautioned not to take this alkaloid to the point of causing dilatation of the pupils.

Morphine should never be prescribed for dysmenorrhea as some of the worst cases of morphinism that I have encountered were due to the administration of this drug for this condition.

In addition to the drug treatment, it is essential to put the patient in the best physical condition possible. Many of these young women are asthenic and underweight. In them, sunlight, fresh air, restricted hours of school or labor are helpful.

Twice in my experience the dysmenorrhea has been so excessive as to require temporary x ray sterilization which, if entrusted to skilful hands, will last only from nine months to a year, during which time of quiescence the patient may recover from the dysmenorrhea

Recently French authors have recommended resection of the presacral nerve which is said to afford complete relief This operation is sufficiently serious not to be recommended lightly Whether it is permanently curative is likewise undetermined

While pregnancy and labor in a large number of cases permanently relieve dysmenorrhea, a certain number of patients are not cured

It should also be kept in mind that acquired dysmenorrhea, appearing well after adolescence, may be due to pelvic inflammation, to submucous fibroids, or adenomyosis, all of which require different types of treatment than the purely "essential" dysmenorrhea discussed in the preceding paragraphs

**Underfunction of the Ovaries (Oligomenorrhea, Amenorrhea)**—Amenorrhea due to cervical or vaginal stenosis requires surgical intervention Cervical stenoses are difficult to overcome, unless of such minor character that dilatation with Hegar's dilators is feasible Where the cervical lining has been destroyed, plastic operations may be attempted with the knowledge that recurrence is frequent. Twice I have been obliged to perform supracervical amputation to overcome the recurrent hematometra Septa and stenoses below the cervix lend themselves readily to permanent cure by vaginal plastics This applies as well to hymeneal closure with resultant "primary amenorrhea" Here it should be kept in mind that hematocolpos and hematometra may be complicated by hematosalpinx The fluid must be let off slowly, irrigation of the vaginal or uterine tract avoided, the patient watched for the first twenty four hours for peritonitic symptoms which signify leakage from the decompressed hematosalpinx into the peritoneal cavity This fortunately uncommon but very fatal complication requires immediate laparotomy with removal of the tubes

Variation of the periodicity and amount of menstrual flow is a common phenomenon even in the most normal women. Persistent oligomenorrhea is of little significance although often considered of great gravity by women. It frequently accompanies minor degrees of health disturbance and not infrequently precedes the onset of amenorrhea, particularly in the obese.

Primary amenorrhea in the adolescent is usually of little significance. The time of onset of menstruation varies so greatly in different ranks of the population, in different racial groups and in different climates, that the absence of menstruation up to the age of fifteen or sixteen rarely brings the patient to the physician.

If seen in otherwise apparently normal and healthy young girls whose physical examination is negative, whose state of health is good, who by rectal examination have been shown to possess internal genitals, and a permeable hymen and vagina, nothing need be done except to counsel proper hygienic measures, which include extra nourishment in the thin and asthenic, moderate restriction of carbohydrates and fat in those inclined to obesity, as well as fresh air, sunlight, restricted school hours, sufficient normal exercise, and when indicated, irradiated cod liver oil. A thorough examination of the chest, perhaps controlled by fluoroscopy or x-ray, to exclude latent tuberculosis may be advisable.

I may say that yearly I encounter from 3 to 4 cases of apparently essential amenorrhea in whom x-ray of the sella turcica demonstrates the presence of a beginning pituitary neoplasm.

Among the adults, the largest group of amenorrhoeic women is formed by the obese. Just why obesity plays such a predominant rôle is not quite clear, and yet the prompt and gratifying response resulting from reduction in weight is too uniform and striking to be accidental. The basal metabolism of these women in the great majority of cases is found to be normal, and the fewest are able to tolerate even moderate doses of thyroid without resulting nervousness and tachy-

cardia Therefore a careful, slow reduction by means of diet is the main and usually effective remedy

It is not sufficient to tell these patients merely to diet The dietary must be carefully planned and gone into in minute detail A marked reduction in the carbohydrate and fats must be insisted upon On the other hand, the protein factor should not be reduced at all (only lean meat) The patient should be instructed to lose weight at the rate of 1 pound a week, this reduction may have to be continued for months or more than a year as individuals weighing 250 to 180 pounds are very frequently met with If this slow reduction by diet is maintained, the patient not only loses weight without feeling weak, but likewise acquires dietary habits which continue throughout her life On the other hand, I have found that the rapid reducing diets not only weaken patients unduly, but that as soon as they have lost 30 or 40 pounds in as many days, they at once revert to their old habits and regain the lost weight as quickly as they have lost it.

Obesity combined with well marked hirsutism signifies a more serious condition Here, loss of weight may not restore the menstrual function In the fewest instances can the cause of the hirsutism be determined, as in adrenal tumors

In the underweight and asthenic our first effort must be to exclude the presence of tuberculosis, diabetes, Addison's disease, etc With these patients a forced diet in which both the protein and carbohydrate factors as well as the fats are stressed and increased, must be insisted upon Frequently, such patients lack appetite. When milk and cream are not well tolerated, beer proves an excellent substitute Such conditions may be noted in psychotic or psychoneurotic patients who because of fashion, revenge motives, or other psychological factors, voluntarily starve themselves Occasionally, the use of insulin helps to increase the appetite and nutrition in these individuals As soon as a normal weight is regained the majority begin to menstruate normally

It should be remembered, as stated under diagnosis, that in pituitary and thyroid underfunction, and late in pituitary and



thyroid overfunction, amenorrhea is a regular symptom. Needless to say, only such measures as will affect the underlying endocrine disease are of use.

The milder types of thyroid overfunction respond gratifyingly to medical measures if the patient can be spared many of the stresses of life. Mild sedatives, such as bromides or luminal, may be taken over long periods of time, in small doses and are sufficient to quiet the excessive nervous reaction, but do not make the patient too inert and sleepy. The severer forms of thyroid overfunction will require diminution of the thyroid mass by appropriate partial thyroidectomy.

In cases in which x-ray shows an enlargement and erosion of the sella turcica by pituitary adenomata, particularly in the silent cases in which no brain pressure symptoms or ocular disturbances are noted, skilful radiotherapy to the base of the skull frequently proves satisfactory and curative. If erosion of the bone is more marked and pressure on the optic chiasm develops, operation followed by radiotherapy is indicated, if for no other reason than to save the eyesight. The result will depend in the main upon whether the tumor is benign (adenoma) or malignant (carcinoma).

My experience with so-called *endocrine therapy* for oligomenorrhea, although it extends over many years and although large groups of cases have been studied, is entirely disappointing. Such results as have been obtained by the use of estrogenic substances (theelin, progynon, amniotin) as well as gonadotropic substances (follutein, antuitrin S, prolan) are fully accounted for by accidental coincidence and are more than duplicated by the cases we have observed over long periods of time, in which menstrual function has become normal without endocrine therapy.

Even in the few instances in which we have used as much as 30,000 to 40,000 M. U. of estrogenic substance, no effect was produced.

The so-called *stimulating x-ray treatment* of the ovaries I have discontinued for a number of years as I consider the treatment too haphazard and entailing considerable danger of

entirely abolishing a subthreshold ovarian function. These underfunctioning ovaries require little additional injury to be put completely and permanently out of function. Therefore, while an occasional case might perhaps be temporarily stimulated, the dangers of the treatment are too considerable to warrant its use.

It should also be kept in mind that a small number of amenorrheas are due to overfunction of the ovaries, the estrogenic substance circulating in the blood being continually high, cases which can only be recognized by means of thorough hormone study. In these cases, certainly, estrogenic substances are not indicated.

To summarize, therefore, the amenorrheas in the present state of our knowledge and with our present armamentarium, are best treated by general and hygienic measures. In my opinion endocrine therapy is entirely ineffective in this group unless there is a marked reduction in the basal metabolism (minus 15 per cent or more), in which case the response to thyroid substance is prompt and while continued, permanent.

**Overfunction of the Ovaries (Premature Puberty, Puberty Bleeding, Menorrhagia, Metrorrhagia, Preclimacteric Bleeding)**—In *premature sexual maturity*, therapy is only effective if the cause is due to ovarian tumor. The treatment in this is purely surgical. The few cases of pineal tumor reported have with one exception been in males. Adrenal tumor, if diagnosable, likewise requires surgical removal. The larger number of children in whom the condition is "essential," require no treatment. Eventually when the real time of puberty arrives, they become normal individuals, often excessively fertile. Such children are shy, oversensitive and require special parental care and minute supervision at school.

*Puberty bleeding* may manifest itself with the first menstruation or may appear after this function has been established for one or more years. This group, of which I have now seen some 30 cases, varies between the ages of eleven and twenty years. The condition, although it may persist for years, is eventually self limited. Among these patients the constitu-

tionally normal, the asthenic and the obese will be found. The common symptom is excessive and prolonged bleeding, with consequent secondary anemia and all of its sequelae.

The local findings, as previously stated, may be entirely normal. It is well, before instituting treatment, to make sure of the degree of anemia, the number of red blood cells, the absence of underlying general blood dyscrasia, thrombocytopenic purpura, or purpura hemorrhagica (platelet count).

These patients, depending upon their general condition, must be relieved of their school or work tasks, put to bed, often hospitalized. If the hemoglobin is below 50 per cent, a transfusion, either direct or citrate, should be given. In former days, I was repeatedly obliged to perform numerous curettages, in several instances to produce temporary sterilization by means of x-ray to the ovaries, and before this measure was known, on one occasion obliged to perform a hysterectomy to save the patient's life.

Today, thanks to the discovery of Dr. Samuel Peck, it has been found that this group in every instance so far, responded to the intra- or subdermal injection of minute doses of moccasin venom.<sup>6</sup> For the details of the treatment I must refer you to the original articles. These patients are injected twice weekly with doses of moccasin venom, beginning with 0.1 cc. of 1:15,000 dilution, gradually increased to 1 cc. of 1:3,000 dilution of this substance. The response is usually noted within two weeks and if treatment is continued for six to eight weeks, a normal menstrual cycle develops. Relapses are frequent, so that it is now our custom to repeat the injection treatments after the elapse of six or eight weeks, and after this second course, to give a third, and usually final, treatment some three months later. A few unusually resistant patients have required 2 or 3 courses of treatment over a year for the last three years but, due to this measure, have remained in perfect health, being able to resume all of their activities.

Where this method of treatment is not available, the older methods, such as repeated transfusions, rest in bed and occasional curettages may tide such patients over long periods of

time until they eventually and spontaneously become well. I no longer feel justified in giving  $\alpha$  ray to the ovaries in order to tone down the excessive bleeding, although at this youthful age no permanent harm need be anticipated if the treatment is entrusted to competent hands. We have had a number of patients who have borne normal children after moderate doses of  $\alpha$  ray have been given to the ovaries.

*Adult group menorrhagia and metrorrhagia* is an extremely common symptom during the age of maturity. In my experience considerably more than 50 per cent of patients suffer from these symptoms from organic causes. Therefore, it is essential to exclude such causes as abortion and its sequelae, pregnancy and its consequences, fibroids, malignant tumors of the uterus and adnexa, pelvic inflammations, before considering an endocrine background. As previously mentioned, this differential diagnosis offers many difficulties.

Let us take for granted that local or general organic causes have been searched for and excluded. In spite of this in the majority of cases the treatment of adult bleeding requires surgical rather than endocrinological treatment.

A few women suffer from excessive and prolonged bleeding because of general blood dyscrasia, especially thrombocytopenic purpura. To arrive at this diagnosis a proper blood examination, including the count of the blood platelets and the determination of the blood coagulation time, is necessary. These cases react brilliantly to the snake venom therapy.

A patient suffering from excessive or prolonged bleeding must be thoroughly examined. In the fewest instances are endocrine stigmata discoverable. In thirty years I have seen 3 cases in which marked reduction of the basal metabolism (minus 20, 25, 35 per cent) was noted in combination with bleeding. All of these cases responded promptly to the administration of thyroid extract. In the great majority, lowered basal metabolism however, produces amenorrhea.

At the onset of the symptoms the usual drugs may be tried, including ergot and cotarnine hydrochloride or salicylate as well as pituitrin injections. Rarely is any curative

effect obtained. Bed rest, ice-bag to the lower abdomen, short (1 quart) hot douches of plain water, may also be used. If in spite of these medical measures the bleeding continues and a pelvic inflammation or infection of the cervix can be excluded, one is obliged to resort to the curet which may prove of therapeutic value but is mainly used for diagnosis.

*Curettage without pathologic examination of the curettings is in my opinion malpractice.* Examination of the curettings in the large majority of cases will show normal endometrium, in a certain number, chronic hyperplasia, which indicates excessive ovarian function. In a few cases a corporeal malignancy will be discovered.

After a thorough and aseptic curettage, one is justified in observing the patient further. Many are relieved over a period of months or years, and I have several patients in whom a number of curettages were performed at intervals of two or three years until they reached the normal menopause. When, however, the curettage proves of no value, the further procedure will depend on several factors.

Women in the late thirties, who have had all of the children that they desire, may be subjected to radiotherapeutic sterilization. The ensuing menopause will be that which would correspond to their normal menopause. I prefer this technic to the insertion of radium into the uterus because it avoids hospitalization, local trauma and the persistent, often long continued leukorrhea which so often follows this method of treatment. However, if radium is more readily available than external radiotherapy, it can be applied in dosage of 800 to 1200 milligram hours, well filtered, by means of an appropriate applicator introduced into the uterine cavity.

In young women it is preferable to repeat the curettage at intervals, rarely more often than once every year. If this proves ineffective, a reduced menstrual flow can readily be obtained by small doses of x-ray applied to the ovarian regions. Radium can likewise be used in doses of 400 to 600 milligram hours although it is more apt to interfere with subsequent pregnancies than radiotherapy.

Again you will note that I pin my faith to other measures than endocrine therapy. In my hands and that of my group we have treated a large number of patients by means of estrogenic and gonadotropic substances. Neither the one nor the other has given us gratifying or concordant results in spite of the glowing recommendations vouched for by many in authority.

In connection with these groups, it should also be kept in mind that a small number of patients who are beginning to suffer from prepituitary tumors (carcinoma or adenoma), others with thyroid toxicosis, in the early stages of these diseases, frequently suffer from menorrhagia and metrorrhagia. Under these conditions, as soon as the diagnosis is made, the underlying disease is dealt with, in case of prepituitary tumor by radiotherapy to the base of the skull or operation, in milder thyroid overfunction by medical treatment of this disturbance, by thyroid resection in those of graver import.

Very occasionally, ovarian tumors in children, sometimes malignant in nature,<sup>1</sup> in adults tumors of various nature, particularly the so-called "Brenner tumor," produces excessive bleeding. When such tumors are discovered, their ablation is, of course, indicated. These tumors produce the excessive bleeding by overproduction of estrogenic substances.

There is another type of overfunction, fortunately comparatively rare, which I have described under the name of *premenstrual tension*.<sup>2</sup> This is not necessarily accompanied by excessive bleeding, but produces extreme psychical and physical tension. The patients complain of unrest, a feeling of tension or pain in the breasts, are unable to control their emotions, lose their temper and poise readily, and usually sum up their condition by saying that they feel like "jumping out of their skin." Their extreme discomfort and annoyance continues until the menstrual flow appears and then, as a rule, disappears as if by magic. The tension may occur over a period of seven to ten days preceding the menses.

A very simple method of treatment, if properly carried out, has proved efficacious. At the time that the menstrual

tension is most marked, usually four or five days before the onset of the flow, the patient, in the morning, takes a full dose of citrate of magnesia. It is best to take no food either solid or liquid until one or two large fluid bowel movements have occurred, then forced fluids—tea, coffee, water or lemonade until  $1\frac{1}{2}$  to 2 quarts have been ingested. A prompt deturgescence of the breasts and great relief from the general psychical and physical tension is thus obtained.

**Why Has "Endocrine Therapy" Proved So Disappointing?**—I am fully aware of the widespread use of "endocrine products." This is no new development. Even thirty years ago, inert corpus luteum, ovarian residue and ovarian extracts were widely employed and their brilliant effects heralded. The results obtained by certain enthusiasts were quite as good as those now claimed for the newer and physiologically potent remedies. The excellence of the results described in the literature is strictly proportional to the enthusiasm, the lack of clinical experience or lack of accurate critique and control of those employing these remedies.

The majority of clinicians fail to take into consideration that the majority of both amenorrheas as well as excessive bleedings are of transient nature and quite self-limited. They are willing to ascribe to their therapy any results obtained even if accidental.

I, on the other hand, have made it a point carefully to watch large numbers of patients belonging to both groups who receive no treatment, and I am able to give equally good statistics, without having resorted to any therapy. On the other hand, I have seen the most absurd, and in some cases harmful misuse of so-called "endocrine remedies." Amenorrhea due to absence of vagina and solid uterus treated with large doses of estrogenic substance, bleeding due to carcinoma of the corpus treated for months with gonadotropic substances, for example.

Spectacular increase in our knowledge of the causes which produce the monthly cycle in the female, as well as the factors which bring about disturbance of the cyclical phenomena,

have been made. These advances which aid in diagnosis have outstripped the therapeutic results so far obtained. It is necessary to caution the clinician against unfounded optimism usually based upon "cures," which are accidental or coincidental in diseases of self limited course.

In my experience, amenorrheas which typify the under functional group, do not respond to direct endocrine therapy except when found in patients with marked reduction of the basal metabolism. Only this small class is relieved by thyroid extract. Treatment of the majority is limited to indirect hygienic and dietary measures.

Patients with menorrhagia and metrorrhagia, on the other hand, can be treated successfully by the standard gynecological procedures, endocrine therapy likewise proving of little or no help.

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## CLINIC OF DR HENRY B RICHARDSON

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### THE RELATION OF THE THYROID GLAND TO GRAVES' DISEASE

THE object of this paper is to emphasize the general aspects of Graves' disease, and to support the point of view held by Marine<sup>1</sup> and others, that the disorder of the thyroid is not the cause of the disease, but rather a secondary effect due to disturbances elsewhere in the body. By Graves' disease I mean a general disturbance, one symptom of which is hyperactivity of the thyroid. Under the term I include the cases in which enlargement of the thyroid is diffuse, as well as those in which the enlargement is nodular, that is to say, I include both exophthalmic goiter and toxic adenoma, following Harington<sup>2</sup> and others. Although it is perhaps objectionable to name a disease after an individual it is much better than employing a term which gives false implications as to the nature of the disease.

In the present discussion I am not including the simple goiters. As is well known these occur endemically in regions in which there is a deficient intake of iodine. It occurs in other localities when for some reason the demand for iodine is increased. The disease can be readily controlled in most cases by the prophylactic administration of small amounts of iodine.

A prevalent idea of Graves' disease is a somewhat mechanical one. The thyroid is thought to enlarge in the first instance, and as a result of this to pour an increased amount

of secretion into the circulating blood, with the production of toxic symptoms. If this were so, there should exist a reverse picture with signs of deficiency, and a primary decrease in the size of the thyroid. This often appears to be the case but probably the small size of the thyroid is caused by atrophy supervening on a preceding hyperplasia. As is well known, thyroid insufficiency is often associated with a goiter. If the increased secretion in Graves' disease were the whole picture, one would expect that the prolonged administration of thyroid extract would reproduce all the symptoms. The tremor, nervousness, tachycardia and signs of an increase in the basal metabolism are, in fact, well known, but the exophthalmos is conspicuously absent. The extract produces creatinuria in man (Krause and Cramer<sup>3</sup>), but neither the creatinuria in man (Palmer<sup>4</sup>) nor the rise in basal metabolism in rabbits (Sturgis<sup>5</sup>) is prevented by the administration of iodine.

Perhaps the argument may be clearer from a consideration of other diseases of internal secretion. Diabetes, for instance, with a decrease in the activity of the islands of Langerhans, is the exact reverse of hyperinsulinism with a tumor of these same cells. Other examples are the pituitary giant and the pituitary dwarf, or the symptoms associated with a parathyroid tumor as contrasted with the effects of removal. With all of these the concept seems to apply, that the hyperactive state is associated with one type of lesion and the hypoactive state with the reverse.

In disease of the thyroid there are many things which cannot be fitted into such a simple scheme. There is no clear clinical and pathologic picture which can be labelled hyperthyroidism and set up as the reverse picture of a thyroid deficiency. In fact, there are several features in common between the so-called "hyperthyroid" and "hypothyroid states." The first is that a hyperplasia of the thyroid occurs in both conditions (Marine<sup>1</sup>, Rienhoff and Lewis<sup>6</sup>). A second fact is that in both, as shown by Marine,<sup>7</sup> there is a marked decrease in the percentage of iodine contained in the gland. The percentage of iodine is inversely proportional to the degree of hyperplasia of

the gland, whether in thyroid deficiency or in Graves' disease. In both conditions the administration of iodine causes the accumulation of iodine in the hyperplastic gland and brings about involution. Chemical analysis of the iodine compounds in Graves' disease has shown that the percentage of the total iodine, inorganic iodine, thyroxine, and diiodotyrosine are reduced. These values are approximately normal after the administration of iodine (Gutman<sup>8</sup>). A fourth feature which is found both in Graves' disease and in diminished activity of the thyroid, is the severe muscular weakness. In Graves' disease this is associated with the appearance of creatine in the urine and a decrease of the normal capacity of the body to retain creatine, analogous to the findings in progressive muscular dystrophy (Shorr<sup>9</sup>). Graves' disease is distinguished by the fact that both manifestations disappear on the administration of iodine. The creatinuria is not parallel to the basal metabolism and may persist in Graves' disease even after the basal metabolism has sunk spontaneously to normal or below. A fifth observation is that the exophthalmos is not always parallel to the severity of the Graves' disease. In New York City it is absent in a striking proportion of cases. On the other hand, it has been known to precede other symptoms such as elevation of the metabolism, it is the last manifestation to disappear after a therapeutically successful thyroidectomy and may even progress to the point of blindness (Naffziger<sup>10</sup>) even though the other symptoms are relieved. The experimental evidence is even more paradoxical. The administration of thyroid extract fails utterly to produce exophthalmos in normal animals (Carlson<sup>11</sup>). The one instance in which exophthalmos has been reported following the administration of the active principle of the thyroid gland, is the work of Kunde<sup>12</sup>. She removed the thyroid from young rabbits, gave them enough thyroid extract to permit growth, allowed them to develop myxedema and on administration of large doses of thyroid extract, observed a marked exophthalmos. This became greatly accentuated when the head of the animal was in a dependent position. Marine Rosen and Cipra<sup>13</sup> succeeded in

producing very marked exophthalmos in rabbits by the use of methyl cyanide, which produces a hyperplasia of the thyroid but causes a decrease in the basal metabolism. In animals from which the thyroid had been previously removed the exophthalmos was invariable. The most startling piece of experimental evidence is the observation of Marine and Rosen<sup>14</sup> that exophthalmos can be produced by the use of thyrotropic principle of the anterior lobe of the pituitary in animals even when the thyroid gland has been removed. It is of great interest that in animals exophthalmos has been produced only in connection with a thyroid deficiency.

Thus the so-called "hyper-" and "hypothyroid states" are similar as to the pathology of the thyroid gland, the percentage of iodine or thyroxine which it contains, the involution of hyperplastic gland by iodine, the creatinuria and muscular weakness. Exophthalmos in man is not parallel to the basal metabolism, and in animals it is best produced in the absence of the thyroid. In spite of these contradictions, however, there is no doubt that states of increased or decreased activity of the thyroid exist.

The foregoing is explicable only on the theory that the hyperplasia of the thyroid is not primary, but takes place in response to some other influences which increase the demand for iodine and for activity of the thyroid gland. According to this, the thyroid responds to unusual demand by a compensatory hyperplasia, which may be excessive and thus produce Graves' disease, or may be inadequate and constitute relative thyroid insufficiency.

This is the theory elaborated by Marine twenty-five years ago. The pathologic basis for it has been substantiated by Rienhoff<sup>15</sup> and It has found acceptance, among others, by Dunhill<sup>16</sup> and Harington<sup>2</sup>.

The difficulty of explaining Graves' disease on the basis of a simple increase in the secretion of the thyroid gland led Plummer<sup>17</sup> to revive the theory that the secretion of the thyroid gland is altered in quality. "The characteristics of exophthalmic goiter may be due to an incomplete thyroxin molecule."

Harrington<sup>2</sup> has criticized this theory, mainly on the ground that the abnormality of the secretion should be capable of demonstration by injection of the pathologic gland into animals. No evidence of a heightened or unusual effect of such glands has been obtained. In fact the activity of such a thyroid is low, as might be expected from its low content of iodine. Harrington also states that "no derivative of thyroxin containing less than the full complement of iodine either approximates to thyroxin in activity or exhibits any toxic properties whatever."

What then are the influences which cause an increased demand for activity of the thyroid? One of these is in all probability "the Graves' constitution." The linear type of individual with vasomotor instability has been well described by Warthin,<sup>18</sup> who also emphasizes the hyperplasia of lymphoid tissue, of the lymph nodes, thymus, spleen and thyroid. This is reflected in a relative lymphocytosis of the circulating blood. The most profound and obvious effect is produced by psychic disturbances. These are present in overt and obvious form in the great majority of the cases. No special training is required to elicit them, only the interest and sympathetic attention of the physician is needed. Other well known inciting causes are puberty and especially pregnancy. The influence of the pituitary is indicated in Case I reported on page 799.

The abnormalities in the creatine metabolism alluded to above are important in the understanding of the disease. They provide also an aid to the diagnosis and an objective test of the severity of the disease second in importance only to the basal metabolism.

The patient with Graves' disease excretes large amounts of creatine (Shaffer<sup>10</sup>) as compared to the negligible quantity found in the urine of normal individuals. The frequency of muscular weakness is well recognized. The connection between these two facts was obscure until the discovery of the part played by creatine phosphate in the physiology of muscle. Every muscular contraction is initiated by the breakdown of creatine phosphate into creatine and phosphoric acid. These products are immediately resynthesized by the use of energy.

derived from another source. The appearance of large quantities of creatine in the urine is, therefore, presumptive evidence of the failure of this mechanism of resynthesis.

The loss of creatine in Graves' disease is important because it is associated with disease in the muscles. Askanazy<sup>20</sup> found widespread degeneration and replacement by fat. This he observed in the skeletal muscles, including the extrinsic muscles of the eye. The author considered these lesions a partial explanation for the exophthalmos and the sole cause for the lack of convergence. In the severe cases the pathologic picture described by him very closely resembles the lesions of progressive muscular dystrophy. Naffziger<sup>10</sup> reported an extreme degeneration of the extrinsic muscles of the eye. These were three to eight times the normal size and "the color varied from a pale edematous half-cooked appearance to a deep red." They were observed at operation in six patients with Graves' disease who had progressive exophthalmos in spite of thyroidectomy. The observation was confirmed by histologic examination, which showed "varying degrees of degeneration of the muscles, fibrosis, and cellular infiltration." Thus the disease constitutes a threat not only to the muscular health of the patient, but to the eyesight as well. Since the creatinuria and the muscular weakness can be relieved by the use of iodine, it is logical to employ the latter for the treatment of exophthalmos as well. Marine<sup>13</sup> has demonstrated in animals the effect of iodine in the prevention of exophthalmos.

In Graves' disease the creatinuria disappears on the administration of iodine (Palmer<sup>4</sup>), in contrast to the findings in progressive muscular dystrophy (Shorr<sup>21</sup>).

In addition to the creatine in the urine severe cases of Graves' disease have a diminution in the output of creatinine to half or even a third of the normal value. The output of creatinine is thought to be an index of the muscular efficiency of the individual. A decrease of this magnitude is indicative of a profound disturbance in the muscles. A causal relation between this defect and Graves' disease is indicated by the fact

that the creatinine returns gradually to normal with the prolonged administration of iodine

The study of the creatine metabolism was extended by Dr Ephraim Shorr<sup>21</sup> of this clinic by putting the mechanism under strain by the ingestion of creatine. The creatine tolerance test which we have employed is as follows

The patient takes a creatine-free diet for three days. On the third day she takes 1.32 Gm of creatine previously dissolved in 180 cc of water. This creatine contains 1 molecule of water of crystallization and is the equivalent of 1 Gm of creatine in the urine, expressed as creatinine. The directions which we use for out patients and the labels on the bottles follow

#### DIRECTIONS FOR THE CREATINE TOLERANCE TEST

1 You will be provided with three bottles, two for the samples of urine which you are to bring to the clinic, and one containing a solution of creatine to be taken as directed. The crystals in the empty bottles are a preservative which is to be added to the bottles in which the urine is collected at the start of each twenty four hour period

2 For one day before and the two days of the test, the diet is to be free of fish, meat and meat products, such as meat soups, etc. No chicken and no cocoa allowed

#### *Collection of Specimens*

1 On arising the second day of the diet, empty the bladder and *discard* the urine. Note the hour say 8 o'clock

2 Collect *all* the urine passed during the next twenty four hours *including* the specimen passed at *exactly* 8 o'clock the next morning. This completes the first specimen. Mix thoroughly, measure to full amount and fill bottle No 1. Note on the label your name, history number, the date and the number of ounces passed during the twenty four hours

3 Now at 8:10 o'clock drink the entire contents of the bottle marked "Creatine"

4 Collect all the urine passed during the next twenty four hours *including* the specimen passed at *exactly* 8 o'clock the next morning. As before mix, measure the volume in ounces, fill bottle No 2 noting the name, history number, date and number of ounces passed

5 Bring all three bottles to the laboratory as soon as possible. Keep the specimens as cool as possible during the collection period preferably in the ice box.

When patients are observed in the hospital it is desirable to collect the urine on the third day, also



## LABELS

(color) *orange*

Urine No 1 Before Creatine Name History No Ounces for day Date
---

(color) *white*

Creatine 1 32 Gm Keep in a Cool Place
---

(color) *green*

Urine No 2 Creatine Day Name History No Ounces for day Date
--

Creatine was determined by the Folin colorimetric method (Hawk and Bergem<sup>22</sup>), creatinine by the method of Benedict<sup>23</sup>. It should be noted that the presence of acetone or diacetic acid in the urine gives a very large positive error. In this case, the urine should be treated by the method of Blau<sup>24</sup>. The nitrogen was done by the method of Kjeldahl and with the creatinine served as a check on the accuracy of the collections. Following is a report of a test in a moderately severe case of Graves' disease

	Creatine	Creatinine
Jan 15-16/34 Control day	0 306	0 508
Jan. 16-17/34 Creatine day	0 711	0 405
Per cent retained		60 per cent
Jan 13/34 Basal metabolism		plus 50 per cent
Jan 20/34 " "		" 40 " "

The creatine excreted on the creatine day minus that excreted on the control day divided by the total amount which might have been excreted, or 1 Gm, gives the percentage retained. Thus in the example above 0.71 minus 0.31 leaves 0.40 Gm of extra creatine excreted. Of a possible 1 Gm, 0.40 was excreted giving a retention of 60 per cent. The normal man retains 80 per cent or over, and the normal woman 70 per cent or over.

The test shown above is characterized by a high output of creatine, a low retention of ingested creatine, and a very low output of creatinine. Disturbances of this severity are encountered mainly in one other condition, namely, progressive muscular dystrophy. Creatinuria in general, however, is met with in a variety of conditions, in normal children in decreasing amount to the age of puberty and even beyond, in pregnancy, febrile infections, starvation, neuromuscular disease, and a variety of miscellaneous conditions (Hunter<sup>25</sup>). Many of these can be readily excluded. In very doubtful cases it is well to repeat the test after the administration of a sedative, such as phenobarbital 0.03 Gm ( $\frac{1}{2}$  grain) twice daily. If the defect still persists iodine should be administered in doses of not more than 30 mg (30 drops of the syrup of hydriodic acid) daily. Improvement in the creatine metabolism is evidence that the defect is due to Graves' disease (or thyroid insufficiency). Often the improvement is progressive over a period of weeks, and as noted above usually includes a gradual increase in the output of creatinine.

**Case L.**—A married woman, New York Hospital No 43343, aged thirty seven was admitted to the thyroid-endocrine clinic on January 4, 1933. She had an outspoken case of acromegaly for fourteen years, which had been stationary for the past few years. Symptoms referable to the thyroid gland were nervousness, loss of 5 pounds in weight with a normal appetite, irritability, and easy fatigue. Her thyroid was diffusely enlarged to the size of an orange. Her pulse was 104. After three weeks' administration of the syrup of hydriodic

acid, 30 drops a day, the pulse fell to 80 and the metabolism to plus 3 per cent. Though the symptoms were not marked, disturbance of the thyroid was indicated by the effect of the iodine. The association of the thyroid with the pituitary is abundantly shown in animal experiments. Certain extracts of the anterior lobe of the pituitary cause a hyperplasia of the thyroid gland, which has even been demonstrated *in vitro* (Eitel, Krebs and Loeser<sup>20</sup>). With the hyperplasia there is a sharp increase in the basal metabolism. This patient is cited as an example of simple and obvious cause for increase of thyroid activity, namely, hyperactivity of the anterior lobe of the hypophysis.

The following case, in a patient of Dr Bruce Webster, of this clinic, illustrates the effect of pregnancy and of psychic influences on the development and course of Graves' disease.

**Case II**—Mrs C, aged thirty, No 9423, October 18, 1932. The chief complaints were nervousness, lack of strength and choking sensation.

*Present Illness*—In 1922 the patient was informed at another hospital in New York that she had a goiter but was told to forget about it. She married in 1927. Although she was always inclined to be nervous she has been much worse in this respect since the birth of her first baby in September, 1929. Immediately after the delivery she felt more nervous, very weak and generally let down. Her neck increased slightly in size. One year after the first pregnancy, her health was almost normal. She began taking iodine after the birth of the first baby and had been taking it intermittently ever since. During the second pregnancy, she vomited a good deal and could not eat. The baby was born at eight months in April, 1932. Again she was more nervous and tired, especially after the delivery. The baby has been considerable care. The patient lost 10 pounds in weight since delivery in April, 1932. Her appetite was good. Palpitation was always present, also dyspnea on exertion. Her feet swelled at night. She had a choking feeling when tired or when eating. She worried a good deal

She had no one to help her with the baby, who was not well, and cried all night

*Physical examination*, October 21, 1932 Height 172.1 cm (67½ inches), weight 59 Kg (130 pounds) Prematurely gray, undernourished young woman Widened palpebral fissure, moderate exophthalmos, slight nystagmus Thyroid diffusely enlarged, slightly nodular, moderately firm Heart rapid and regular Systolic murmur heard Pulse 110 Liver edge palpable Reflexes hyperactive Fine tremor of hands

On October 25, 1932, she was seen in consultation with Dr Nellis Foster Her basal metabolism was plus 67 per cent, in a satisfactory observation Operation was advised She could not come to the hospital, however, as there was no one to take care of the baby

In November, 1932, the baby was found, at the New York Hospital Department of Pediatrics, to have no cerebral hemispheres November 10th, no decision as to disposition of the baby In January, 1933, the patient reported that she had been able to sleep more while the baby was at New York Hospital and had recently slept eight hours a night, although the baby was home again The patient gained 3 Kg (6.6 pounds) and was less nervous and less fatigued

The baby died of lobar pneumonia in February, 1933 Two weeks later the patient's basal metabolism was plus 27 per cent and the pulse 88 On April 4, 1933, it was plus 15 per cent On September 26, 1933, she had gained 10 Kg (22 pounds) Her pulse was 80, compared to 120 when first seen, blood pressure 120/68 Her basal metabolism was minus 11 per cent The thyroid was firm and much decreased in size No iodine was taken at any time The only medication used was phenobarbital

This case is extraordinary, if not unique It illustrates first, the association of symptoms of Graves' disease with each of two pregnancies, most striking after parturition Second, it illustrates the continuation of symptoms in association with worry over an idiotic child and a complete spontaneous cure following the death of the infant The two factors which in

creased the demand for thyroid activity were pregnancy and emotional stress

If Graves' disease is in fact a response of the thyroid gland to increased demand for thyroid secretion, there should exist, in addition, two analogous conditions. The first, a hyperplasia of the thyroid with thyroid insufficiency, is well known. The second also occurs, namely, an increase in the demand for thyroid secretion, with a compensatory increase in the activity of the gland just sufficient to maintain the metabolism within normal limits. Many cases of postoperative Graves' disease reach a state in which the symptoms persist in spite of a normal basal metabolism. The same thing sometimes occurs spontaneously as the result of a slow regression of the disease. The following case, Dr Shorr's, is a probable illustration of early unoperated Graves' disease, without increase in the basal metabolism

**Case III**—Miss N, aged nineteen, New York Hospital, No 43674. Admitted to surgical pavilion on October 14, 1933

*Chief Complaint*—Difficulty in swallowing

*Family History*—Both mother and sister are nervous

*The menstrual history* was normal prior to the onset of the present illness

*Present Illness*—The patient had a sore throat and dry cough in December, 1932. Following this she felt a difficulty in swallowing because of a sensation of a lump in the throat. Then she began to be nervous and upset over little things. In April, 1933, a physician told her that she had a goiter, and gave her a solution of iodine, 10 drops, three times a day, without relief. Then she began to have attacks of palpitation with some precordial pain and dependent edema on standing. She noticed, also, some protrusion of the eyes and blurring of vision on physical exertion. Her menses became irregular, sometimes four or five days late, or omitted. The lump was larger at times. She has had many sore throats and also attacks of

hoarseness with occasional brassy cough for the past ten or twelve months. She had lost 14 pounds in the same period. The basal metabolism in June, 1933, was plus 7 per cent, in August, plus 11 per cent. About this time she again received drops, to shrink the goiter. She has had pain in the right arm for three weeks.

Additional symptoms were excessive perspiration, tremor, diarrhea at intervals, and easy fatigability.

*Personal*—Dr Shorr elicited the history of a distressing and humiliating family situation. The father was a drunkard and terrified the family and insulted the guests. He caused the breaking of her engagement just before the onset of her present illness.

*Physical Examination*—Both lobes of the thyroid gland were enlarged, the right more than the left. The isthmus was palpable. The enlargement was soft, diffuse, the size of a lemon. The trachea was deviated slightly to the right. There was a very little fine tremor of the fingers. The hands perspired in the palms. The heart rate was 130. Otherwise the physical examination was negative. Weight 42 Kg (93 pounds), height 162 cm (5 feet, 3½ inches).

#### *Basal Metabolism*

October 11 1933	Plus 5 per cent
October 16 1933	Minus 2 per cent
October 23 1933	Minus 2 per cent
November 8 1933	Minus 4 per cent

The urine and the Kline diagnostic and exclusion tests for syphilis were negative. The red blood cells were 4,000,000 and the hemoglobin 95 per cent. The white count was 11,000, later 9800.  $\alpha$  Ray of the lungs was essentially negative. The heart shadow was unusually narrow and elongated and of the hypoplastic type.

The creatine tolerance was

Dec 1-9 1933	Creatine Gm./24	Creatinine Gm./24*	Remarks
Control day	0.120	1.35	No medication
Creatine day	1.035	1.505	
Retention 8.5 per cent.			

Since in the normal woman the creatinuria does not exceed 0.06 Gm a day and since the quantity normally retained is 70 per cent or over, the disturbance in the creatine metabolism was very profound

On December 28, 1933, the patient was given a prescription for 30 drops of the syrup of hydriodic acid once daily (30 mg of iodine) On March 15th, this was changed to 10 drops three times a day, and this was continued until her most recent visit on June 21, 1934

The creatine tolerance changed as follows

Dec 7-9, 1933	Creatine Gm /24°	Creatinine Gm /24°
Control day	0.065	1.675
Creatine day	0.402	1.302
Retention 56 per cent		
Jan 19-21, 1934		
Control day	0.006	1.126
Creatine day	0.208	1.168
Retention 80 per cent		

Thus, it changed from the picture which is characteristic of Graves' disease to normal. It should be mentioned that there was an improvement in the family situation and in the condition of the patient.

On January 18, 1934, she was considerably better although most of the symptoms were present in milder form. Pulse 100, weight 46.3 Kg (101.9 pounds). Tachycardia still present. Hands were cool and moist. Medication continued without change.

On March 15, 1934, the patient continued to feel very much better than on admission. She was still tiring easily and was short of breath, but this was less marked and she had been able to return to her work running a machine in a textile mill, eight hours a day. Weight stationary. She had noticed that her eyes were less prominent. Tremor practically absent. Palpitation rare and only on excitement. The situation at home was a little better and the patient had begun to assert herself, feeling more independent with the earning of some money. The father was no longer drinking because he had not the

whereas the patient could not see any possibility of a radical change for the present in the family situation

On physical examination, the patient looked quite well. She was composed, quiet and more cheerful. Her eyes were normal in appearance. The conjunctivae were a little red. The heart rate varied 80 to 106. No murmurs. Still overacting. Thyroid. Moderate enlargement of all lobes, quite firm, not tender. Extremities. Tremor +, no edema. Basal metabolism plus 12 per cent. Creatine tolerance normal.

On April 26th, the patient was not quite so well, but on June 21, 1934, she showed a continuation of the improvement. The basal metabolism was plus 1 per cent. The creatine tolerance continued normal.

All the symptoms of Graves' disease were present in rather mild degree in a single woman of nineteen, beginning with infection and developing under stress of an intolerable family situation. Fairly typical signs were encountered on physical examination. The basal metabolism ranged from plus 5 per cent to minus 2 per cent and reached plus 12 per cent only after very marked clinical improvement, falling later to plus 1 per cent. Objective evidence of Graves' disease consisted in the spontaneous excretion of creatine and the very low creatine tolerance, both of which cleared up, along with clinical improvement, on the administration of iodine. We are presenting this case, therefore, as a probable instance of Graves' disease with a normal level of the basal metabolism.

The influence on the thyroid gland of factors other than the thyroid itself, namely, constitution, puberty, pregnancy, acromegaly and psychic influences, demand consideration in the treatment of the disease. So far as they are temporary they should influence the decision whether to employ radical or conservative methods. It is obvious, for instance, that Graves' disease occurring at puberty should be treated more conservatively than a case of the same severity occurring in adult life. The same applies to cases which begin during or shortly after pregnancy. If, further, the onset is associated with a difficult



personal or economic problem which is temporary or amenable to treatment, then again the tendency should be toward conservatism. Unfortunately, the patients who suffer from Graves' disease appear more adept at getting into difficult situations than at getting out again. Nevertheless, no form of treatment, whether by iodine or surgery, is complete without attention to the factors mentioned.

According to the conception of Graves' disease described above, surgical treatment must be regarded as illogical, because it does not strike at the root of the disease. Nevertheless, it is highly effective in the majority of cases, and is the only justifiable treatment in cases which are at all severe. Early and mild cases, particularly in younger individuals, are sometimes successfully treated over long periods by the continuous administration of iodine in small doses, *i. e.*, 15 mg (15 drops of the syrup of hydriodic acid)\* a day. We have found no evidence of injury by such a dosage. We believe that the danger of "escape" has been exaggerated, and that many patients go on indefinitely with a basal metabolism well below the initial level.

The "escape" from iodine might be caused by (a) a decreased effectiveness of the iodine, and (b) an increase in the severity of the disease. The escape is commonly thought of as "iodine fastness," similar to that which occurs with quinine in malaria. We believe that it is due not so much to the iodine as to an increase in the severity of the disease, resulting from one of the inciting causes mentioned above, particularly psychogenic factors. At most, iodine provides a material which is essential for the manufacture of thyroxine. In patients who have had marked remission of symptoms with iodine, we have frequently seen a sharp rise in the basal metabolism, the result of a known emotional stress, and a subsequent fall when the cause was removed. Not infrequently, the transfer of a patient from a disturbing environment to an atmosphere of

\* This preparation is desirable because it is dilute enough to measure accurately. It is pleasant to take, in contrast to the disagreeable taste of Lugol's solution. The effect of the iodine is the same in all preparations.

efficient hospital care has a reassuring effect, which is reflected in a fall of the basal metabolism even when iodine is continued. After all, there is no reason why the exacerbations and remissions, which are so prominent a feature of the disease before treatment, should cease merely because of an increase in the ingestion of iodine.

We believe, also, that if for any reason it is necessary to withhold iodine, a second remission can be induced within a short period. Indeed, we have evidence of a renewed iodine effect in as short a period as eight days. Presumably, small doses are excreted more rapidly than the relatively enormous amounts often used before operation.

If the fear of iodine has been exaggerated, and if the chance of "escape" overestimated, it follows that there is no need for operating very soon after the administration of iodine is begun. Indeed, the delay may be an advantage to the patient. Marine (1911)<sup>1</sup> showed that the greater the degree of involution of the thyroid, the safer the operation. In decompensated cases, moreover, delay may be desirable to allow the circulation to rest. We have observed several patients with whom for one reason or another the operation was postponed up to a period of six weeks. These seemed to withstand the operation with remarkably little reaction. For these and other reasons, it is desirable when setting the time for operation to avoid a stereotyped routine.

Before using iodine in preference to surgery, the physician should satisfy himself that no ill effects will result from omission of iodine or "escape" from its effects. He will have in mind, of course, the possibility of cardiac damage, particularly in older persons.

Persistence or recurrence of symptoms after operation is not uncommon. The most obvious indication of this is that some patients come to operation more than once. Others, though not in good health, do not require a second operation although careful observation shows evidence of the persistence of the disease. The inquiry should include subjective symptoms of thyroid insufficiency as well as hyperactivity. At

tention should be directed especially to muscular weakness and exophthalmos. Special care should be taken to elicit inciting factors, particularly psychogenic influences in the immediate environment. Objective tests should include as a minimum. The pulse, weight, physical examination, basal metabolism, creatine tolerance, observation of exophthalmos (preferably by means of an exophthalmometer) and measurement of the ability of the eyes to converge.\*

Attention to inciting factors, particularly psychogenic influences, is just as important in the treatment after operation as before. Muscular weakness frequently persists and has the same significance as before operation. Both the weakness and the metabolic defect disappear on administration of small amounts of iodine.

The most important symptom is exophthalmos, because it continues to threaten the vision of the patient. It will be found to recede or to remain stationary under the administration of iodine. The indications for the latter are not altered by the operation.

Regeneration of the remnants of the thyroid is not at all uncommon. It is also observed in the normal dog after removal of a large part of the thyroid, and can be prevented by the use of iodine (Marine<sup>7</sup>). Since iodine is effective in the prevention of goiter and of thyroid hyperplasia it is entirely logical to continue its use after operation.

In the foregoing it has been pointed out that the fear of iodine is exaggerated when given in small doses, even before operation. Such fear is even less justified after operation when the bulk of the thyroid has been removed. In this we are confirmed by Haines<sup>27</sup> of the Mayo Clinic who has reported uniformly good results from the administration of iodine, over

\* The convergence can be readily measured by the technic of the ophthalmologist. The patient is asked to look fixedly at a flashlight. The examiner observes the reflection of the light on each cornea, while he brings the light steadily closer to the patient's eyes. The break in convergence is readily noted by a motion of the reflection with respect to the cornea. The distance of the light to the bridge of the nose is then measured. Inquiry should be made to exclude gross muscular defects of long standing.

periods of years, in postoperative recurrence of Graves' disease

In conclusion, one may quote the statement of Marine<sup>1</sup> "The essential physiological disturbance of the thyroid in exophthalmic goiter is insufficiency, its reaction compensatory, and its significance symptomatic" Evidence in favor of this principle has been presented above A rational therapy of Graves' disease must include attention to the factors which lie outside of the thyroid gland

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## CLINIC OF DR. LOUIS C SCHROEDER

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#### THE TREATMENT OF PNEUMONIA IN INFANTS AND CHILDREN

THE treatment of pneumonia presents many pitfalls. One of the most flagrant of all medical mistakes, the treating of a disease rather than the caring for a patient, is encountered more frequently in this particular field of therapy than in any other. Recent advances in the study of pneumonia have tended, unfortunately, to make this even more likely and it is only the more conscientious who see the patient first and the micro-organism afterward.

This mistake, when made with infant or child, is more apt to end tragically than obtains with adults. The ease with which small children develop gastro-enteritis, otitis media, and lymph node enlargement in the presence of infection makes doubly incumbent upon the practitioner the necessity of not thinking exclusively in terms of lung pathology. When one considers the extreme lability of the water balance and the ease with which the alkaline reserve is diminished, the difficulties become still more apparent.

The treatment of pneumonia demands, therefore, the most meticulous attention to many so-called "little things." Before considering the purely pragmatic features of therapy, some attention must be paid to certain general aspects of the disease as it is encountered in infants and children.

#### THE PROPHYLAXIS AND THE EPIDEMIC NATURE OF PNEUMONIA

Whether in the home, the hospital, the school or the camp, children having pneumonia must be considered as having a contagious disease and should be isolated. To do less is to

court danger The facility with which it spreads varies from the rapidity with which it can attack a dozen pupils in a school dormitory, to its much less frequent spread in the home

Certain mistakes are committed in the name of isolation and they bear comment Giving the name "isolation" to a ward or pavilion confers no sacred prophylactic or curative powers upon it Much more than mere baptism is required Witness the following as an example of the violation of the ordinary rules of common sense

A patient, ill with pneumonia, was admitted to a university hospital where the rule is that all pneumonias must go into an isolation pavilion Due to overcrowding, he was placed in a ground floor corner room where the noises from the intersection of two busy city streets vied with the intermittent clashing of machinery from a respirator, containing a child ill with poliomyelitis, a short distance down the corridor Sleep was an utter impossibility Hospital red tape, being of an exceedingly tough fiber, is difficult to cut and it required a good deal of maneuvering to secure a room in the general hospital where, not only was it possible to secure sleep, but even more easy to effect perfect isolation, without endangering life

In the home, the problem of isolation differs from that in the hospital, being dependent upon the economic status of the family and its general intelligence To isolate a child properly requires, at times, a Puritanical conscience because the influx of relatives and well wishers is certain to be at once a nuisance and a danger It is worth securing, however, as it is a sound hygienic measure and will provide more quiet

The details of isolation should not be ignored Clean hands, a clean, healthy mouth and nose, and the wearing of gowns are paramount A nurse, doctor or attendant who has the slightest upper respiratory infection has no business in the room of a sick child Gauze masks have a doubtful value, while the use of germicidal mouth washes is worth little more There is no justification for running the risk of irritating mucous membranes with them when normal salt solution will

clean without irritation. Carriers of pneumococci are in a different category and one is fully justified in using germicidal solutions in an endeavor to free them.

The small child may have to be taught the use of the paper or gauze handkerchief, but, no matter what the age, provision should be made to see that all secretions are rendered harmless. All personal effects, whether dishes, clothing, or bed linen, must be kept separate and then boiled.

How is one to judge when a case is no longer contagious? Negative throat cultures for the pneumococcus and the Streptococcus hemolyticus are usually reliable but not infallible. Two weeks after defervescence is not too short a time to wait even though a throat culture may be negative before that time has elapsed.

Prophylactic measures for infants and children include their periodic physical examination, the regulation of house, school and outdoor hygiene, with especial reference to the prevention of fatigue. Chilling must be avoided when humanly possible but, if encountered, such measures as warm baths, drinks and rest should be instituted. No evidence which can be considered conclusive makes the diet anything but a slight factor in causing respiratory infections. A strong impression exists, nevertheless, that a too high percentage of carbohydrate is a responsible factor. Vitamin A alone is a weak reed on which to lean, although the use of cod liver oil during the winter months has much to recommend it.

The damage done to children by persons who have colds is almost incalculable. Children's parties especially for youngsters under seven are too often veritable breeding spots. In proportion, they are as damaging as school rooms where sniffing, coughing children are present.

Last, but by no means least, take care of the child with even a trivial upper respiratory infection. Seldom is more than rest indoors necessary.

A philosophical consideration of the problem of isolation and prophylaxis of pneumonia by the general practitioner may cause him to doubt the need of so much caution, particularly



when he dwells upon the many cases of pneumonia which he has treated with never a contact case having developed. It is true that epidemics are usually confined to the pneumococcal variety and that they occur only when large numbers of children are together. Notwithstanding all this, a serious study leads to the conviction that all the details here considered are necessary, and the inevitable conclusion drawn that measures useful for the many are fully as valuable for the few and worth all the trouble their use may involve.

### TREATMENT

**Sleep and Rest**—If there is one thing which can be valued above everything else in the treatment of pneumonia, it is sleep and rest. Noise and excitement have a more deleterious effect upon children than is usually recognized. Among too many adults the impression exists that children thrive on noise. Only those who have followed children closely know how fallacious this is.

To secure rest and quiet for a child is more difficult than it is for the adult. Many parents feel that unless something is being done constantly for their children, they are being neglected. Aunts and uncles see a golden opportunity to bring in the latest mechanical toys—the noisier, the better. The unwise ministration in attempting to make the child laugh is still another example of the many things done that are bad. Lay persons are not the only offenders. Not infrequently, children are examined too often. Once a day is certainly enough to go over any child and the physician's explanation of his reason for limiting examinations will often carry more weight than an expressed demand for quiet. The petulant, spoiled youngster who is not sick enough to be prostrated, but who is more quiet in his mother's arms, should be permitted to have his way. This does permit, in easy fashion, the changes in position that are so desirable.

Summed up, complete rest is assured by choosing the most quiet room, having in mind the value of sunlight and ease of ventilation, by limiting the number of examinations, by the

exclusion of all visitors and by the omission of every therapeutic measure for which there is no cogent reason. Securing a quiet nurse who knows the value of nursing care in pneumonia is a desideratum, unfortunately, not always obtainable.

**The Diet and Fluid Needs**—Uncomplicated pneumonia is a relatively short disease and to figure caloric needs and attempt to meet them is frequently wasted effort. Nor is it necessary to attempt to give a diet which has the perfect proportion of nutritional elements. If, for any reason, however, the period of illness extends beyond ten days, these observations do not hold. If they did, the same mistake would be made which for so many years caused typhoid fever to be such a formidable problem.

It is logical to think of the diet in pneumonia from the standpoint of furnishing quickly available energy, of preventing dehydration and acidemia, and of minimizing gastrointestinal irritation.

At once, it becomes apparent how desirable it is to furnish as large a proportion of sugars and starches as is consistent with freedom from intestinal upsets. One need not be unduly alarmed by the fear that they cause abdominal distention. This unfortunate and rightly dreaded complication is much more frequently the result of a partly parietic bowel, probably from a lowered vasomotor tone, than from dietary indiscretions. Fermentative diarrheas hark back to the days when milk was not the clean commodity it usually is today. The sugars have been improved tremendously and one no longer has to depend upon questionable grades. To be sure, one can still raise well infants using commercial granulated sugar, but one has a distinctly safer feeling, in the presence of disease, when a combination of sugars, such as dextrins and maltose, can be employed.

That there is a need for protein nobody can seriously question. There is a negative nitrogen balance because of the albuminous exudate and it is usual to find an increased uric acid and creatine output even before the temperature falls. Nevertheless, the time element is the factor which makes it

seem wiser to think in terms of preventing an acidemia rather than of meeting protein loss

Salt-free diets are recommended by some because of the usual retention of sodium chloride in the body, although the exact site of the retention is not definitely known. Others suggest an increased sodium chloride intake, either by adding lime water to the milk or extra salt to the food, justifying this attitude by pointing out that the blood chlorides are usually low. The latter viewpoint seems more reasonable, and one should at least furnish the usual complement of salt, if not convinced that extra salt is necessary.

With some children, unaltered cow's milk is a problem. Lactic acid, peptonized, or evaporated milks are useful in these cases. Any one of these three suggested forms diminishes the chances of intestinal disorders and all are ideal for the addition of the desired sugar. One to one and one-half pints of milk daily is the usual intake.

Food itself really plays a less important part than fluids. With the kidneys working under a severe handicap, with the skin dry and hot and the entire heat-regulating mechanism out of gear, one must figure on at least 15 per cent increase over the estimated need for fluids of the healthy child.

Practically, this means that the infant over six months of age should be offered daily from 2 to 2½ ounces of fluid per pound of body weight, and from one to two years, 2 ounces per pound of body weight. From two to six years, the goal should be between 3 and 4 pints, and, past six years, at least 2 to 3 quarts.

One pint of milk with an added ounce of sugar, a mixture of 8 ounces of orange juice, 8 ounces of water, and an ounce of sugar, plus 1 pint of plain or alkaline water or weak tea, make a base from which to start all children who are not on formulas. As conditions warrant, add cooked cereals, gelatin, junket, custard, grated egg yolk, double toasted bread, plain crackers, and plain puddings. Meat or meat broths and egg albumin water had better not be given.

The excellent results which have followed the use of paren-

teral fluids in acute intestinal intoxication have led to their more widespread employment in other conditions. Hypodermoclyses of normal saline or 4 per cent glucose, up to 20 cc per pound of body weight, or the intravenous use of the same substances reducing the amount to 10 cc. per pound but not more than 300 cc at one time, are sound therapeutic procedures in pneumonia where there is fluid need or threatened or actual collapse. Intravenous glucose is usually given in 6 or 10 per cent solution, the stronger concentration being used when kidney function is distinctly impaired. Rectal drips of tap water and nasal drips are not very satisfactory while the intraperitoneal route, with the ever present threat of abdominal distention, is not recommended. Keeping close track of the daily intake and output of fluids for either infant or child, and the testing of the elasticity of the skin, especially in infants, are always to be borne in mind. Hypodermoclysis in pneumonia should be given elsewhere than on the chest wall in order to avoid embarrassing the excursion of the chest wall. The loose tissues of the anterior or lateral surfaces of the thighs is a suitable place.

No one can write a blanket diet to cover all cases of pneumonia in children. The constant recollection of the vital need for fluids and the value of carbohydrates are the two things of major importance. After that, individual needs must be met as they arise.

**Fresh Air**—Some twenty years ago, it was the fashion in many children's hospitals to put every case of pneumonia outdoors irrespective of age, the condition of the child, or the clemency of the weather. This was a laudable attempt to prove that cold air was the most desirable adjunct in therapy. It is to be hoped, however, that such an attempt will never be made again. Actual coldness of air plays but a minor part. It can scarcely be doubted that a temperature of 68° F in air that is moving slowly and thus is free of drafts is the one with which to start. It may well be that some older, robust children will stand lower temperatures, but certainly with infants and small children low temperatures are to be avoided. The stuffy

room wreaks more havoc in pneumonia than in any disease and must be avoided at all hazards

**Oxygen.**—In analyzing some 225 cases of pneumonia treated at the New York Nursery and Child's Hospital during the past few years, nothing has been more satisfactory than to observe the beneficial effect of efficient oxygen therapy To those of us who go back to the days when a funnel was held a few inches from the nose while oxygen was supposedly being administered, the development of the tent and of the nasal catheter method has come as a revelation The slightest blueness around the lips or the fingertips should immediately bring up the question of the advisability of using oxygen If mild, one can use a nasal catheter intermittently or continuously Make sure that the nose is as free from obstruction as possible Cocaine, epinephrine, or ephedrine nasal drops will help The oxygen tent is, of course, the ideal method The tent must be watched constantly as an oxygen concentration beyond 45 per cent is undesirable while overheating is an ever-present danger

Among the laity, the oxygen tank has long been the symbol of an approaching end As a plain matter of fact, it usually was Owing to our deeper appreciation of the value of oxygen used earlier, more frequently and with greater efficiency, it will not be long before the old symbolism will have disappeared

The only jarring note which can be struck is to question the value of adding carbon dioxide to the oxygen Anybody who has had experience with cyanotic newborns knows the difficulty of ascertaining just what the cause of the cyanosis is and how conservative one must be in judging the effects of any given therapeutic measure Considering now, however, only cases of aspiration pneumonia or atelectasis, the opinion is expressed that it is more desirable to depend upon oxygen alone This opinion is grounded on the fact that not infrequently in these cases the mixed airs have a smothering effect, whether the carbon dioxide is a 5 to 10 per cent mixture and causes more struggling This is only an opinion, but worth bearing in mind, and the question, here brought forth, is deserving of more study

**Transfusions**—From the day Lindeman devised his needles and took transfusions out of the category of major operative procedures, there has always existed a fear that in pneumonia, one should not transfuse because the right side of the heart could not stand the brunt of an extra load. That certainly is an ungrounded fear as far as infants and small children are concerned.

The ease and efficiency with which a good intern staff can perform transfusions in infants has settled beyond question their tremendous value to a pediatric service. In a free city hospital one sees more frequently the type of child who needs a transfusion at the beginning of pneumonia than one does in the average private practice. In the series mentioned before about 30 per cent of the children were transfused one or more times. Far from being a cause of danger they were almost invariably beneficial. Frequently, there was a drop in temperature, and a marked general improvement. These were not always maintained, but nevertheless for the small child who does not represent a particularly good risk, transfusions will often throw the balance in the right direction. For those cases which are threatening from the very start or develop serious vasomotor weakness, fear of embarrassing the circulation by a transfusion can be discounted completely.

For a single transfusion give 10 cc. per pound of body weight but a greater amount than 250 cc. should not be given. The value of transfusions has only lately begun to be appreciated. Given with due regard to typing and slow administration, whether citrated or direct, one can expect the transfusion to bring certain benefit.

**Drugs**—It is quite the fashion to condemn offhand the use of drugs in pneumonia. Chosen with due regard to dosage, indications, and the possibility of causing gastric upsets, however, they can play a distinctly helpful rôle. The unsavory reputation of drugs is due, for the most part, to errors. Chief among these is the giving of adult cough mixtures and fever powders in what is presumed to be a child's dose. These combinations are supposed to relieve cough or reduce fever,

whereas, they seldom do because they upset the stomach first. One drug at a time for children is a good rule to follow. Thus, for cough codeine can be depended upon. At six months of age give  $\frac{1}{16}$  to  $\frac{1}{12}$  grain every three or four hours, at one year  $\frac{1}{12}$  to  $\frac{1}{8}$  grain, at two years  $\frac{1}{8}$  grain, and beyond six years  $\frac{1}{4}$  grain. That it has a distinctly quieting effect, also, is an added reason for its use.

Combinations of phenacetin, acetylsalicylic acid, caffeine and Dover's powders are not to be given to children even in the first stage when there is usually a great deal of distress. One will usually find that acetylsalicylic acid alone will reduce fever and relieve distress in the first trying hours as well as any of the combinations. Give one grain for each year, every three or four hours, but do not allow more than five doses.

Atropine is extremely useful especially in the presence of a copious secretion or bronchial spasm. Always explain to mothers the possibility of flushing and even a febrile reaction, otherwise there will be the difficulty of explaining why the disease is not scarlet fever. Under a year and a half of age give  $\frac{1}{1000}$  to  $\frac{1}{750}$  grain every three or four hours, and over that start with  $\frac{1}{750}$  to  $\frac{1}{600}$  grain.

Compound tincture of benzoin in steam inhalation must be used at times for laryngeal spasm or stridor. Its continuous use, especially when much mucus is present, is seldom indicated because of the danger inherent in breathing moisture-laden air. It is better to use it for half an hour every two hours and then make certain that any relief obtained is not at the expense of flooding the lungs.

Sodium perborate should be employed regularly to keep the tongue, mouth and buccal membranes clean. Desiccated dirty membranes are a fertile field for micro-organisms and fungi. All cleaning should be done gently, especially with infants.

Digitalis should not be used routinely. No evidence justifies it. There are no studies in children at all comparable with those made with adults by Wyckoff at Bellevue Hospital and it would seem to be the wiser course to apply to children

the conclusions there drawn until direct evidence favoring its routine use is forthcoming

That digitalis has no place in the therapy of pneumonia is, of course, not true. In chronic carditis or heart failure it should be used and in vasomotor collapse there can be no criticism if one does try its effects, although it is now quite generally conceded that the heart itself is not at fault so frequently as has been imagined in the past.

Once the decision is made to use digitalis—and this should never be made lightly—it is much the best plan to digitalize and then supply a daily maintenance dose. At the Nursery and Child's Hospital, Dr. May G. Wilson outlined a method for digitalization of children in connection with her cardiac clinic. Through her kindness I am permitted to give, previous to publication, the outline which has been prepared and which is just as useful in cardiac failure from pneumonia as in rheumatic carditis, the field of digitalis use which has been most frequently explored in children. The Preparation Tablet No. 1 (Lederle) is, of course, not the only one now available but it serves as an example. The outline follows.

#### DIGITALIS MEDICATION IN CHILDREN

Preparation Tablet No. 1 (New York Heart Association)  
(Lederle)

0.05 Gm	$\frac{1}{2}$ cat unit	( $\frac{1}{4}$ grain)
0.1 Gm	1 cat unit	( $\frac{1}{2}$ grains)
0.2 Gm	2 cat units	(3 grains)
0.3 Gm	3 cat units	(4 $\frac{1}{2}$ grains)

#### Any Tincture (Standardized)

1 cc.	1 cat unit	(15 minims or 30 drops)
2 cc.	2 cat units	(30 minims or 60 drops)
3 cc.	4 cat units	(60 minims or 120 drops)

#### Dosage

Eggleston	15 cat unit per pound	Adults
Pardee	2 minims to 3 minims per pound	Adults
Davidson	$\frac{1}{2}$ grain per pound	Children
New York Nursery and Child Hospital	$\frac{1}{2}$ cat unit per pound	Children
	or $\frac{1}{2}$ cc per pound	Children
	or $\frac{1}{2}$ grain per pound	Children
	or .03 Gm per pound	Children



*Routine Method used in Cardiac Clinic, New York Nursery and Child's Hospital*

Two cat units every six hours for 4 to 8 doses total 8 to maximum 16-24 cat units

Stop on toxic symptoms Give daily maintenance dose of 1 to 2 cat units a day 1 to 3 grains

*Rectal Administration*

Slow—2 to 4 cat units in 1 ounce water every six hours

Rapid—4 to 8 cat units in 1 ounce water every six hours

The idiosyncrasies of individual children, the necessity of avoiding excitement, and the necessity of maintaining an adequate dose to produce results, make the administration of digitalis to children one of extreme care and thorough observation, but the above outline will allow anyone to use digitalis with confidence and, above all, get results as all good preparations are now marked in cat units

The drugs used for stimulation and emergencies are those usually employed for adults Alpha lobeline, epinephrine, camphor, and caffeine are the ones generally relied upon, the first two often being used intracardially in collapse and all of them by the hypodermic route as a rule

**Serum Treatment**—There can be no question that for pneumococcus Type I lobar pneumonia a specific is available and should be used With all other types, the use of sera, in children at least, must be looked upon in the light of a hopeful wish

The use of the Type I serum is not quite as general as it should be To say that the death rate for lobar pneumonia is so low in children that it is not necessary to use a proved remedy is a curious kind of twisted reasoning It overlooks entirely the very important fact that he who practices medicine must be as much concerned with shortening the length of any disease fully as much as he is to avoid an unfavorable outcome Especially must this strike home with peculiar force on those who have charge of children With all our vaunted progress nobody has the slightest inkling of what the ultimate effect is, in later life, of the many infections that children endure

Typing of pneumococci has reached the point where it is

done quickly and effectively and no matter how small the community, provision can be made to determine the type and administer the serum within forty-eight hours of the onset, the best time for its administration

Always do an intracutaneous skin test, using 0.1 cc. of the serum diluted ten times with normal saline. The extent of the reaction will be the guide as to the amount to be given in the first intravenous dose. The total amount to be given in the first twenty-four hours will vary from 200 to 800 units per pound of body weight, depending upon the severity of the invasion and the size of the reaction. A safe starting dose for infants is 2 cc. and for children over five years, 5 cc. Subsequent doses and the intervals between will depend upon the drop in temperature in the first six hours. If less than one degree, double the next dose and divide the remainder of the total between the next two doses at six to eight hours later. Practically, it works out that infants will get from 5 to 10 cc every twenty-four hours and children 15 to 25 cc. Menir advises the giving of one dose after the temperature has remained below  $100^{\circ}\text{F}$  for two to four hours and has never used more than a total of seven.

**Routine Care**—One daily cleansing bath with soap and one daily emptying of the bowels are necessary. Secure the latter either by giving routinely, milk of magnesia, or a mineral oil, preferably in a flavored jelly form. When necessary, a low enema of 4 to 6 ounces of sodium bicarbonate or plain water is just as efficacious as the soapy mixture frequently employed. The rectal mucous membrane can and frequently does become irritated from soap. Change the position of the patient if he does not do so himself and avoid sitting up whenever possible. Take the temperature at three-hour intervals and order a tepid sponge if it is over  $104^{\circ}\text{F}$ . Apply cold only to the head. Cold applications to the skin defeat their own purpose by further limiting an already lowered evaporative power of the skin. Avoid mustard plasters and counter irritation to the skin when the diagnosis is fully established.

## COMPLICATIONS

The complications which occur in pneumonia are as varied as with adults with the addition of a larger percentage of the unfortunate sequelae which follow aspiration, either at birth or from swallowing foreign bodies, the tonsillectomy accidents and the lipoid degenerations from the unwise administration of nasal oil drops. In order to avoid clouding the issue no attempt has been made to differentiate the various types of pneumonia. The unfortunate infant who has inhaled amniotic fluid presents one type of pathology as clearly different from a straight Type I pneumococcus lobar pneumonia as can possibly be imagined. Nevertheless, the principles underlying the treatment of any type are the same and it seems much wiser in discussing treatment to have the whole child in mind first, last and all the time.

This in no wise takes away from the practitioner the responsibility of settling in his own mind whether the type is bronchial, lobar, or the result of a foreign body. Neither does it lessen his interest in the specialized cases of chronic pneumonia whether they be interstitial or on a tuberculous basis.

**Abdominal Distention**—Insert rectal tube, apply turpentine stupes frequently and revalue diet with the idea of reducing starch and milk intake. If not relieved use surgical pituitrin, starting with 3 minims for an infant and repeat or use a larger dose in two hours if necessary. Peppermint or other medicated enemas are permissible at any time.

**Otitis Media**—The majority of ear drums show some inflammation during the course of a pneumonia. Be sure of definite bulging before incising.

**Diarrhea**—Use protein milk or discontinue all milk. Avoid all roughage in diet. Give from 1 drachm to  $\frac{1}{2}$  ounce of castor oil. Irrigate bowel with from 1 to 2 quarts of sodium bicarbonate water.

**Empyema**—Be quick to aspirate, but slow to operate. Depend upon the former to relieve the embarrassed respiration until the toxic symptoms have disappeared. The thicker the exudate the more likely will resection of a rib be required.

**Delirium** —Ice-bag to head Chloral hydrate and sodium bromide by rectum, 6 to 10 per cent glucose intravenously Tepid sponges Guard against self injury

**Plugging of bronchus**, evidenced by absence of air in lung involved, sudden cyanosis and sudden collapse The plug may sometimes be dislodged by putting the patient into an almost vertical position and slapping the back Bronchoscopic examination in competent hands may prove to be life saving

**Vasomotor Collapse** —Tranfuse or give 6 per cent glucose intravenously Epinephrine, camphor or caffeine hypodermatically Elevate foot of bed Oxygen continuously if anoxemia is evident Bandage extremities Digitalize if cardiac failure seems imminent.

**Lung Abscesses and Bronchiectasis** —In infants and children these complications have been shown to occur more frequently than have heretofore been thought to be the case To treat either well is seldom within the range of any one man's skill The increased interest in, and the constantly improving technics of thoracic surgery are making the outlook for these cases far from being the hopeless proposition they once were One can find in the literature almost a dozen medical methods of treatment varying from postural drainage to the use of drugs and another array of surgical methods varying from compression by wax to lobectomy These hardly come within the scope of this paper but should be read by those who have such cases under their care

#### CONVALESCENCE

This period of the disease is apt to be neglected and this is a grievous fault. Iron or liver extract for a short period is not infrequently necessary The secondary anemia fraction of liver gives good results in children and many excellent preparations of iron are now available If copper is left out as much good will probably be done as if it be added

One should not be satisfied with anything less than the full aeration of the lungs To get small children to breathe deeply

is almost impossible. The familiar blow bottles or balloons can be used by older children and it should be remembered that their use is not limited to post empyema or pneumothorax cases. Infants or small children may be made to breathe more deeply if gentle compression is made downward on the abdominal muscles three or four times a day for varying lengths of time.

The value of cod liver oil, heliotherapy, proper food, and change of climate are too well known to need stressing.

Before dismissing any case as cured one must make certain that he has considered more facts than are included in the statement that the temperature is normal and bronchial breathing has disappeared. If he does not he shall be committing the same mistake against which a warning was issued in the opening paragraph—the mistake of thinking of the disease first and the child afterward.

## CONTRIBUTION BY DR. GEORGE H. HYSLOP

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### MIGRAINE SUGGESTIONS FOR ITS TREATMENT

THERE is so extensive a literature of migraine that a brief clinic on the subject is certain to be inadequate. However, one may be excused for attempting a short discussion of its treatment in the light of certain concepts which have developed within the last decade.

The word "migraine" has traditionally been applied to a certain type of paroxysmal recurrent headache, but now the term has broader implications, and the concept has been extended to include various other manifestations of transitory "paroxysmal" nature, such as some varieties of tachycardia, atypical Ménière attacks, and pseudo appendicitis. In addition, transient mental disturbances or psychic equivalents have been described.

With each advance in our knowledge of pathogenesis, the new information is directed toward unsolved problems. Plausible relationships may be described. During the past ten years or so, the literature of allergy has furnished facts which suggest that migraine phenomena are the result of vasomotor spasm which may be the reaction to some toxin. The precipitating toxin may be exogenous or endogenous. With patients in whom there seems to be a reciprocal relationship between epileptiform seizures and migraine, the attacks suggest that there is a constitutional reactive tendency which may express itself in more than one clinical manner.

As an instance, can be cited the case of a woman who had typical migraine until the menopause. At this time the headaches ceased and grand mal epileptiform attacks commenced.

She was found to have diabetes mellitus. The epileptic attacks stopped when her diabetes was under control. However, even if this be true, and no matter what other forms of acquired factors may be present, there is ample ground to believe that there is an inborn constitutional element. When one considers the frequency of migraine, it is not unlikely that every person possesses some degree of predisposition. The family histories of many sufferers show a strong hereditary background. A common personality trait is a high strung, tense, emotionally sensitive make-up. It is of clinical interest to find that many writers observe that a migraine patient is seldom dull intellectually.

If one grants that a hereditary element is common, it is still true that in some instances no demonstrable inherited basis can be shown. I recall a woman in her fifties, whose personal and family history was free from not only migraine, but the well-recognized forms of allergy. She suffered a left-sided hemiplegia, with the lesion affecting the right thalamus and superior peduncle. Coincidentally, and for two years up to the time I saw her, she experienced frequent typical migraine headaches, with the pain on the right side of her head. Neurologists have learned that in certain instances brain tumors seem to develop out of long existent migraine.

There are numerous biochemical and endocrine abnormalities which have been recorded as related to migraine. I think that many of these abnormalities—or deviations from the average—are perhaps only symptomatic of a general constitutional defect. For this reason, efforts to cure migraine by attention to some one or more clinical or laboratory measured deviations may fail.

There are many uncontrollable variables affecting the balance of vital functions and health. If to predisposition to migraine there be added vegetative nervous system instability, endocrine imbalance, emotional maladjustment, metabolic disease, focal infection, or certain systemic diseases of infectious character, it is understandable that effective control of migraine may be a practical impossibility.

To be specific, one may see a patient whose migraine is influenced by one or more of a number of somatic abnormalities—such as sinus infection, food sensitization, cryptic focal infection, defective liver function, or an underactive thyroid gland. In such an individual, the development of emotional maladjustment will reflexly affect the vegetative and endocrine functions, and contribute to the occurrence of symptoms previously due chiefly to somatic defects. I recall a man who occasionally would have a migraine headache several hours after eating pork. By testing, he was found to be sensitive to a large number of articles of food. He could eat pork with out trouble if he was in good condition. But he was sure to have a headache if he ate pork when tired or under emotional stress. He could avoid pork, but he could not exclude from his diet all the foods to which he showed sensitivity. And, even with the best of mental hygiene, he certainly could not escape all the mental and emotional hazards of life.

In a recent editorial in the Journal of the American Medical Association,\* it was suggested that the riddle of migraine might be solved by focusing attention on the one factor common to all cases—and saying "This must be the psychic factor." There is no proof that emotional maladjustment is universal in patients with migraine. It is not at all scientific to assume that because many migraine patients have personality make ups which are suggestive of the psychoneurotic, their migraine attacks are a specific reaction to psychic disorder. It would seem to me a highly hazardous doctrine that would permit one to disregard the evidence that there are definitely hereditary and somatic acquired factors in migraine.

I have said nothing specific about the treatment of migraine. I do not believe that there is any specific treatment. On the other hand, if it is fair to predicate hereditary predisposition, and if in predisposed individuals various somatic and psychic stresses may serve to upset the equilibrium of an already unbalanced or irritable vegetative nervous system, then real treatment of the disease consists in detecting, evaluating and



removing factors which seem to act as precipitating or aggravating causes. The use of foreign proteins has been disappointing.

Patients with migraine should be told that their symptoms may not be susceptible of relief without intensive and protracted study and observation. It is probably not only cheaper, but more effective in instances of very frequent and severe migraine, to place the patient under hospital observation, which will include the performance of all indicated laboratory examinations.

The symptomatic treatment of an attack of migraine is of importance chiefly in patients whose suffering is intense and lasting twelve hours or more. In some individuals there is a warning of impending attack, and a number of measures seem to be useful in aborting its development. The sedative drugs with or without one of the coal-tar analgesics are commonly used with success. The relatively recent revival of the use of ergot, in the form of ergotamine tartrate or "gynergen" is of interest. A single oral dose of "gynergen" is  $\frac{1}{60}$  grain. The drug may be used continuously two or three times a day. In order to abort or relieve a headache, a single dose by mouth is often adequate. The drug may also be given hypodermically, the dose being about  $\frac{1}{120}$  grain.

In cases in which food tolerance is a probable precipitating cause, prompt evacuation of the bowels is necessary.

With a few patients it is necessary to administer codeine or morphine.

Operation on the middle meningeal artery has been reported in a few instances, but is a decidedly experimental procedure, and should be considered only in the most intractable and crippling cases.

## CLINIC OF DR. EDWARD TOLSTOI

FROM THE NEW YORK HOSPITAL AND THE DEPARTMENT OF  
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### THE USE OF THE LIBERAL CARBOHYDRATE DIET IN THE TREATMENT OF DIABETES MELLITUS

THE use of liberal amounts of carbohydrates in the treatment of diabetes mellitus is a subject of great interest at present. Much has been written recently regarding this method of therapy and though its use is not universal, many clinics favor its adoption because of the excellent results reported from various parts of this country as well as abroad. It may, therefore, prove profitable to consider the factors responsible for the development of this method of treatment, and further consider the findings which have a direct bearing on the problem and which may enable us to reach a conclusion concerning its soundness. In addition, I propose to discuss in detail the preparation of diets which have proved satisfactory, not only from the physician's viewpoint, but that of the patient as well.

The oldest reference concerning the treatment of diabetes with carbohydrate cures is recorded in the Papyrus Ebers. This document dates from approximately 1500 B. C. and antedates the birth of Hippocrates 1000 years. The "medicine to drive away the passing of too much urine" consisted of concoctions from mixtures of cakes, wheat grains, fresh grits, honey, sweet beer, and berries. This was a temporary measure lasting from one to four days.<sup>1</sup>

The next advocate of a carbohydrate cure for diabetes mellitus was Thomas Willis.<sup>2</sup> He recommended milk, rice, starchy

and gummy foods. He also limited the patient to a diet of milk and barley water boiled with bread. This treatment had its beginning in the seventeenth century. The method was not readily accepted. From that time until 1868 there is not much written concerning the carbohydrate cure. It was then that the rice cure of Von Düring<sup>3</sup> was announced. This diet contained groats, barley and oatmeal besides 80 to 120 Gm of rice. In addition he prescribed 250 Gm of meat, moderate quantities of stewed fruit and a small allowance of stale bread and wine. An analysis of this prescription reveals the diet as one of low protein content as well as low in total calories.

Mossé<sup>4</sup> in 1898 was the next to introduce another carbohydrate cure. This was in the form of liberal portions of potatoes. He allowed as much as 1500 Gm a day. The patient enjoyed this diet because of the feeling of satiety it produced. Its reception was not enthusiastic.

At about this time Von Norden<sup>5</sup> observed that some diabetics with vague gastro-intestinal disorders, to whom he gave oatmeal, showed definite improvement in their diabetes. In these cases the excretion of glucose increased at first, but gradually with the continuation of the oatmeal diet the glycosuria fell and remained at a low level or disappeared. Clinically, the patient felt better, and not only did the oatmeal exert a beneficial effect on the glycosuria, but it also decreased the output of ketone bodies. This chance observation was repeated, and after a careful study Von Norden announced his oatmeal cure in 1902. The underlying mechanism was not understood but the results were so striking that its employment was justifiable. This diet or cure, like others before it, had a definite drawback. It was monotonous. No one doubted the value of such one-sided diets as temporary measures, but it was difficult to appreciate their usefulness as permanent régimes.

It occurred to Falta<sup>6</sup> that perhaps combining the various cereals with the potato diet might make the diet more palatable and attractive. He, therefore, enlarged on the individual cures. In principle, the multi-cereal diet varied little from the single cereal one. His diet contained bread, wheatmeal, oat-

meal, rice, potatoes and also vegetables. The protein was low, as animal protein in the form of meat, milk and eggs was excluded. The various carbohydrates were prescribed in the form of soups and farinaceous foods. He also used cereals freely, with vegetables for variety on certain days. Falta observed that on this type of diet the mild diabetic did well. The moderately severe diabetic, however, could not be desugared rapidly. From the observation of patients on such a carbohydrate cure, Falta postulated that high carbohydrate rations, with exclusively vegetable protein restored the carbohydrate mechanism, enabling it to utilize sugars more readily, thereby diminishing the production of ketone bodies. This hypothesis is extremely interesting and is similar to the one upon which the present day high carbohydrate diet is based. Falta's observation regarding the employment of such a diet in the moderate and severe diabetics has been confirmed in our clinic and elsewhere. Today, the difficulty of treating the severe diabetic with liberal carbohydrate rations is solved with the aid of insulin.

The above clinical reports are striking, but even though many remarkable results were presented, the use of carbohydrate cures failed to win universal acclaim. There was considerable evidence against starch-containing foods in the treatment of diabetes. Furthermore, not only were the glucose-containing foods considered deleterious, but also glucose-forming foods, the proteins were to be kept at a minimum. From reasoning such as this the evolution of a diet low in protein and carbohydrate was logical. To furnish the patient with the required calories, fats were freely used. Often enormous quantities of fat were prescribed. This would control or diminish the output of sugar, but it would increase the production of ketone bodies, a fact which was not looked upon with favor. It was observed, however, that *the less* food the diabetic consumed, the greater the improvement of his diabetes. This latter observation led clinicians to change the diet of the diabetic patient to a formula of low protein, high fat, and low carbohydrate, the total quantity being the smallest

compatible with the patient's comfort. Often the patient's feelings were not considered at all. He was given a diet which was minimal in total calories and the patient had to adjust *himself* to the diet.

With all such juggling of diets there was not a single diet acceptable to all. The principle of the smallest possible total quantity or undernutrition, however, was considered desirable and with this factor as a common denominator it was believed that any dietary combination might prove of value. The one-sided high carbohydrate diet appealed to some, the low protein, high fat and low carbohydrate diets appealed to others, but all observers recorded the most striking results when the total calories were kept at a minimum. This clinical observation was definitely established as sound by the work of Guelpa<sup>7</sup> and by the experimental and clinical work of Allen<sup>8</sup>. The undernutrition method gained popularity as certain data revealed the marvels of these low caloric diets. The urine became sugar-free. The ketone bodies disappeared. The patient lost his thirst, and other clinical symptoms of diabetes vanished, yet the patient appeared unhappy. He wasted away. His strength left him. His feet became swollen and from his point of view, the cure was more of a hardship than the disease. Such an appalling situation worried the physician and stimulated him to seek more satisfactory diets. A diet that would keep the patient's urine sugar-free and yet maintain him in a good state of nutrition was the ideal. It was during this period that the discovery of insulin by Banting and Best<sup>9</sup> helped to solve the problem for the diabetic and the physician. Not only did the use of this hormone enable the starved, emaciated and comatose diabetic patient to get a new lease on life but it opened many roads for investigation.

With insulin available Sansum,<sup>10</sup> Geyelin,<sup>11</sup> and Porges and Adlersberg<sup>12</sup> almost simultaneously, though geographically distantly separated, suggested a nearly normal type of diet for the diabetic patient. The patients were consequently given more food than they ever had before with sufficient insulin to insure its utilization and maintain the urine free

from sugar. The diet was so revolutionary that its composition is worth stating. It contained protein 100 Gm, fat 125 Gm, carbohydrate 250 Gm. The insulin requirements were enormous—as much as 200 units daily. This régime was most acceptable to the patients. It proved expensive, however, and for some unknown cause it did not win over many physicians even though it definitely established that a diabetic can live on a diet of nearly normal composition, provided sufficient insulin is used with it. The diet was considered particularly advantageous in the treatment of children, whose growth demands many calories. At this point the pendulum began to swing again toward the liberal portions of carbohydrate in the diet of the diabetic, and clinical, as well as experimental, evidence was brought forth which tended to establish the soundness of this procedure.

Porges and Adlersberg<sup>1</sup> noted that the diabetes among peasants was not as severe as of those in the city. They examined the diets of both groups and since the former contained much more carbohydrate and less fat, they attributed the mildness of the diabetes to that factor. It was also observed that diabetics whose carbohydrate rations were not too low, *even though a glycosuria existed*, lived longest,<sup>12</sup> that a marked reduction of the carbohydrate may induce coma, that limitation of carbohydrate in the diet of the older diabetic, particularly those presenting evidences of cardiovascular disease, may induce anginal attacks,<sup>14</sup> and, it was also established that normal individuals and animals show, for a short time a diminished tolerance to carbohydrate when living on a *low* carbohydrate diet. The experimental evidence on this point is extensive, consequently only 1 portion will be given.

Malmros<sup>15</sup> in a superb presentation of experimental data definitely supports this view. He worked with normal human beings whose tolerance to glucose he tested following ordinary mixed diets as well as after diets *low* in protein and carbohydrate but high in fat. These diets lasted from one to twenty-three days. In every case a decrease of the tolerance for carbohydrate was noted irrespective of the duration of the preceding

diet Greenwald, Gross and Samet<sup>10</sup> were of the same mind Porges and Adlersberg<sup>12</sup> also brought forth considerable evidence demonstrating clearly that high fat, low carbohydrate diets lower a normal person's tolerance for glucose About five years ago I<sup>17</sup> had the opportunity of studying the carbohydrate tolerance of two men whose diet for one whole year consisted of *meat* only, essentially a high fat, low carbohydrate diet Their ability to metabolize carbohydrate as judged by the glucose tolerance test was definitely diminished After two weeks of a normal diet their tolerance to glucose returned to a level considered normal While most of the experimental evidence was confined to normal individuals, it was inevitable that some of the work should be applied to diabetic patients The theoretical grounds for its use were logical and attractive It was deduced from the experimental evidence that the normal carbohydrate mechanism requires adequate daily stimulation and if this stimulus is withheld the insulin-secreting function lags behind It is obvious why the trend of diabetic therapy again began to swing from the low carbohydrate to the higher carbohydrate-low fat diet The latter not only affords ample carbohydrate, but it keeps the total calories low Rabinowitch<sup>18</sup> has had much success with the high carbohydrate, low-calorie—low-fat diet and its use at our clinic is practically the same as proposed by Rabinowitch The principle of underfeeding is maintained and the carbohydrate fraction of the diet is liberal Most of our patients receive 150 to 200 Gm carbohydrate daily, and to some occasionally up to 300 Gm are allowed Patients receiving the higher carbohydrate rations nearly always require insulin The quantity may often be no greater than 20 to 25 units daily, but the fact remains that insulin must be given Rarely, a patient needs only 10 to 15 units to be sugar-free but that is the exceptional case, and given such a case, I feel that it is more practical to decrease the diet and eliminate insulin

The question of undernutrition needs some qualifying I do not mean that every patient should receive so little as to induce emaciation The patient should be given sufficient

caloric intake to keep him looking well, feeling well and satisfied, and yet maintain his weight a few pounds below the accepted standard for his particular type. This of course implies that the very thin diabetic will be built up, and it further implies that the obese diabetic will be given a diet which will induce loss of weight. Each case must be individually treated. The aim in each instance is an optimum weight for that particular individual.

Having presented the evolution of the present-day diabetic diet which is liberal in carbohydrate and low in fat, and the clinical as well as the experimental evidence for its acceptance, I shall now discuss the method in detail, and illustrate its operation.

Before prescribing any diet certain definite standards must be adopted. Some clinics teach the patient the use of scales, so that all the prescribed food may be weighed, some use household measures in the preparation of the diet, some use various size blocks as a basis for comparison. The patient uses these until he mentally fixes the size of the portion allowed. In addition all sorts of calculators and charts have been proposed to help the patient in the preparation of his diet. All the methods proposed are of value. We prefer the use of household measures in the preparation of the patient's daily food intake. This method is simple and requires no special equipment. The patient is taught *what* to eat and *how much*, and since he has always been accustomed to thinking of cups, saucers, teaspoons and tablespoons in connection with food the use of such units as the basis for dietary computation does not prove burdensome.

The nature of the disorder is explained and the necessity for cooperation stressed. The patient is taught how to examine his urine and administer insulin to himself if necessary. In addition to verbal instructions and an actual demonstration the following printed directions are given.



## DEPARTMENT OF MEDICINE

*Metabolism Department*

## TEST FOR SUGAR IN THE URINE

- 1 Buy Benedict Solution
- 2 Place 8 drops of urine (using a dropper) into a test tube
- 3 Add a teaspoon of Benedict's Solution
- 4 Place into a pot of *boiling* water for five minutes
- 5 Let cool and note change
- 6 Blue clear—no sugar  
Green cloudy—little sugar  
Pea green—moderate  
Yellow, to red or brown—very much sugar

## DEPARTMENT OF MEDICINE

*Metabolism Department*

## INSULIN INSTRUCTIONS—SYRINGE AND CARE

- 1 Buy an insulin syringe with 2 needles gauge 24
- 2 Always keep wires in needles when not using
- 3 Before using take syringe apart and boil with needle for five minutes
- 4 Cool and put together
- 5 Wash cap of insulin bottle with alcohol using a piece of cotton
- 6 Push needle through and draw ordered dose
- 7 Wash arm with alcohol
- 8 Pinch skin and inject

We also have a set of waxed food models to acquaint the patient with the actual size of the portion ordered. The models are of considerable help but not indispensable. We allow approximately  $\frac{2}{3}$  to 1 Gm of protein for each kilogram of expected weight for adults, and  $1\frac{1}{2}$  to 2 Gm for children. We also aim at 25 to 35 calories per kilogram. The caloric need of the child is, of course, greater. The carbohydrate fraction is liberal and the fat is minimal. The figures for the total calories are not exact. They are average and in most cases will satisfy the requirements. In attempting to determine the patient's expected weight it is not necessary to adhere carefully to tabulations. If the patient has been thin all his life or has been of average weight prior to the onset of his diabetes it is desirable to use his prediabetic weight, or a figure slightly

smaller, as the basis for calculating his protein and total caloric needs. Should we meet an individual who has been very well nourished before the onset of the disorder and even though there has been a loss of weight, he still appears somewhat obese, the calculations are made on a weight basis which we expect the patient to attain. If, therefore, the patient's weight is 90 Kg and the average weight for his height is about 70 to 75 Kg then all computations are made on the latter figures.

We ascertain the patient's dietary habits and economic status so that the prescribed foods are within his budget and are no different from what other members of the family eat. We avoid the prescription of special trays and dishes. These are not necessary. It is wiser to begin with a slightly lower caloric intake than calculated and as the diabetes shows clinical and laboratory improvement the diet is gradually increased, meeting the patient's caloric needs and keeping his weight at a certain optimum level. Actually we keep a bit below as most patients are inclined to eat more than prescribed. In the hospital and outpatient department the diet is ordered in terms of protein, fat, and carbohydrate, and the dietitian translates the prescription into terms of meals. The patient is also given some instruction in the preparation of diets. This system is most satisfactory when the luxury of a dietetic service is available. If one cannot have this help then the physician must instruct the patient how to select his meals. He must tell him what kinds of food to eat and the quantity of each. This can be done by following the directions given below.

In prescribing for the ambulatory patient considerable latitude is used. He is given a wide choice and the carbohydrate content of the food is expressed in groups of 5, 10, 15, 20 Gm per portion allowed. To give the patient a more concrete idea such portions are compared to lumps of sugar, so that a given serving of food may be equivalent to 1, 2, 3, 4, lumps of sugar, 1 lump of sugar being equivalent to 5 Gm of carbohydrate. The subjoined table illustrates the point in question and the photographs help to give one a clearer idea

of the magnitude of the portion The values in the tables are average and not absolute

TABLE 1\*

GROUP A—Each serving represents about 5 Gm of carbohydrate or 1 lump of sugar

Asparagus	6 stalks	Beet greens	$\frac{3}{4}$ cup
Cabbage	1 $\frac{1}{2}$ cup	Cauliflower	$\frac{3}{4}$ cup
Celery	4 stalks	Cucumber	8 slices
Egg plant	2 slices	Lettuce	$\frac{1}{4}$ head
Pepper	1	Radishes	12
Sauerkraut	$\frac{3}{4}$ cup	Spinach	$\frac{3}{4}$ cup
String beans	$\frac{3}{4}$ cup	Tomato	1 (fresh)
Mushrooms	$\frac{3}{4}$ cup	Tomato	$\frac{3}{4}$ cup (stewed)
Rhubarb	$\frac{3}{4}$ cup	Cantaloupe	$\frac{1}{2}$ medium

GROUP B—Each serving represents about 10 Gm of carbohydrate or 2 lumps of sugar

Beets	$\frac{3}{4}$ cup	Blackberries	$\frac{3}{4}$ cup
Carrots	$\frac{3}{4}$ cup	Cranberries	$\frac{3}{4}$ cup
Pumpkin	$\frac{3}{4}$ cup	Gooseberries	$\frac{3}{4}$ cup
Squash	$\frac{3}{4}$ cup	Grapefruit	$\frac{1}{2}$
Peas (fresh)	$\frac{3}{4}$ cup	Orange	1
Peas (canned)	$\frac{3}{4}$ cup	Strawberries	$\frac{3}{4}$ cup
		Peach	1 small

GROUP C—Each serving represents about 15 Gm of carbohydrate or 3 lumps of sugar

Apple	1 small	Pineapple	2 slices
Apricots	1 small	Plums	3 medium
Blueberries	$\frac{3}{4}$ cup	Raspberries	$\frac{3}{4}$ cup
Cherries	$\frac{3}{4}$ cup		
Puffed wheat	$\frac{3}{4}$ cup	Bread (white or dark)	1 slice
Corn flakes	$\frac{3}{4}$ cup	Uneddas	3
Puffed rice	$\frac{3}{4}$ cup	Saltines	5
Shredded wheat	$\frac{1}{2}$	Graham	2
Wheaties	$\frac{3}{4}$ cup		

\* Miss Flora Pieper of the Nutrition Staff was good enough to prepare these tables as they are used in instructing patients Her help is gratefully acknowledged

GROUP D—Each serving represents about 20 Gm. of carbohydrate or 4 lumps of sugar

Beans, lima	$\frac{1}{2}$ cup	Apricots dried	6 halves
Beans, baked	$\frac{1}{2}$ cup	Banana	1 medium
Corn canned	$\frac{1}{2}$ cup	Prunes dried	2 medium
Corn fresh	1 medium ear		
Potato	1 small		
<hr/>			
	Oatmeal	$\frac{1}{2}$ cup	
	Cream of wheat	$\frac{1}{2}$ cup cooked	
	Wheatena	$\frac{1}{2}$ cup	

The values for meats, cheese and fish are not given. These are prescribed as "average servings," and roughly contain 20 Gm of protein and 15 of fat. It is also advantageous to know the food values of certain other common foods, such as eggs, which average about 6 Gm of protein and 6 Gm of fat, milk which contains about 6 Gm of protein, 8 Gm of fat and 10 Gm of carbohydrate per glass, and that a level teaspoon of butter is equal to about 5 Gm and a level table spoon to about 15 Gm of fat. We prescribe the use of milk wherever the diet permits and we recommend a daily ration of 3 to 4 glasses for a child and about 1 to 2 glasses for the adult.

It is obvious that such crude prescriptions may give rise to considerable variation but usually not significant enough to militate against their use. With such directions the patient can select his diet without confusion, and, furthermore, his meals need not be prepared at home. He can obtain the foods allowed anywhere, no matter where he is, as household measures are nearly always available.

The following case illustrates how the diabetic patient prepares his own diet by following the directions given above. The physician need help only by prescribing the approximate amount of protein, fat, and carbohydrate. I shall give the history very briefly as it is the main purpose to deal with the treatment. The patient, a female diabetic twenty two years

1 SERVING = 1 LUMP  
OF SUGAR

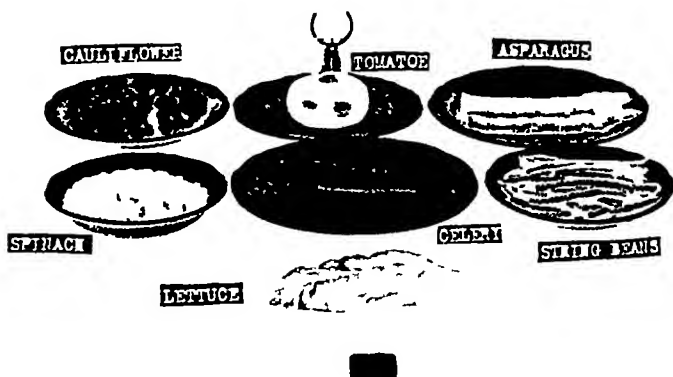


Fig 87—Each serving of the above vegetables contains about 5 Gm of carbohydrate

1 SERVING = 2 LUMPS  
OF SUGAR



Fig 88—Each serving contains about 10 Gm of carbohydrate. The two dark objects represent beets

old, typist by occupation, was referred to the outpatient department from the hospital. Her weight was 102 pounds



Fig 89—Each serving contains about 15 Gm of carbohydrate

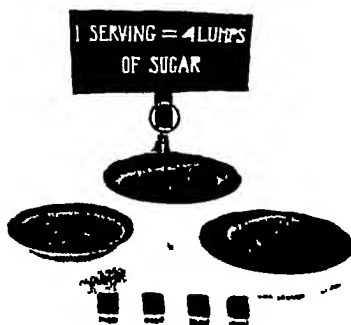


Fig 90—The above portions of banana potato cereal contain about 20 Gm of carbohydrate

The highest blood sugar, while in the hospital, was 357 mg per 100 cc and on admission there was a 4 plus sugar reac

tion and a 2 plus acetone in the urine Her breath had an acetone odor The symptoms of diabetes were of three to four weeks' duration and hospitalization was advised, because of the marked glycosuria and ketosis After a sixteen-day stay in the hospital she was discharged Her diet at the time of discharge was protein 60, fat 90, carbohydrate 150-200, with an insulin allowance of 25 units before breakfast, 10 units before lunch, and 10 units before dinner (25-10-10) On this plan she did not excrete any sugar and her fasting blood sugar and cholesterol values were 136 and 234 mg per 100 cc respectively, and she showed a gain in weight of 4 pounds



Fig 91—These represent the average servings of meats and cheese.

The patient's prediabetic weight was 118 pounds and she was of average height Her parents were not overweight She was active and wished to resume work Her home was about 20 miles away from her place of business, necessitating daily travel Since the patient's weight for two to three years before the onset of her diabetes was 118-120 pounds and since she always felt well at that weight level, the calculation of the diet is based on this figure and *not* on her weight at the time of admission to, or discharge from the hospital On a weight basis of about 60 Kg we arrive at our two basic figures Protein 60 Gm, and total calories 1800 to 1900 (allowing 1 Gm of protein and 30 to 35 calories per kilogram)

The above caloric intake is our aim, but for practical purposes we start with a lower value, and since we wish the fat content of the diet to be low and the carbohydrate liberal, the following approximate formula was suggested Protein 60 Gm, fat 50 Gm, carbohydrate 250 Gm and an insulin dosage of 20-0-15 This diet permits about 1600-1700 calories It was desirable to eliminate the noon dose of insulin if possible as a matter of convenience to the patient One must fully appreciate that all dietary regulation and insulin dosage at the beginning is experimental If the patient happens to be free from sugar, feels well and holds her weight on a given diet everyone is satisfied If, however, the symptoms of the diabetes persist on a given diet and insulin dosage, then the carbohydrate fraction is reduced or the insulin dosage increased until a sugar free urine is obtained and the patient feels well The blood sugar and cholesterol are next studied The patient presented remained sugar free on the trial diet and insulin dosage prescribed so that by gradually increasing the diet the proportions of protein 60 Gm fat 50 Gm and carbohydrate 300 Gm were reached The units of insulin were decreased to 15-0-10 The patient is gaining weight Her fasting blood sugar after two weeks of the above diet was 103 mg per 100 cc. She examines her urine specimens and records the results She administers her own insulin and has had no unfavorable reactions which she has been taught to treat in the event they occur

The patient leads a perfectly normal existence in every respect She takes great interest in the preparation of her diet and this is the way she does it She is permitted about 60 Gm of protein, 50 of fat, and 300 of carbohydrate Since she plans for three meals she divides the carbohydrate allowance into three portions of 100 Gm each Now for breakfast she will choose a portion or two of fruit, in the units advised She may then decide to have some cereal, also bread and milk The carbohydrate values of these foods are clearly shown in the table on pp 840-841, so that no difficulty is experienced in reaching the total ration allowed at one time The values of



## BREAKFAST

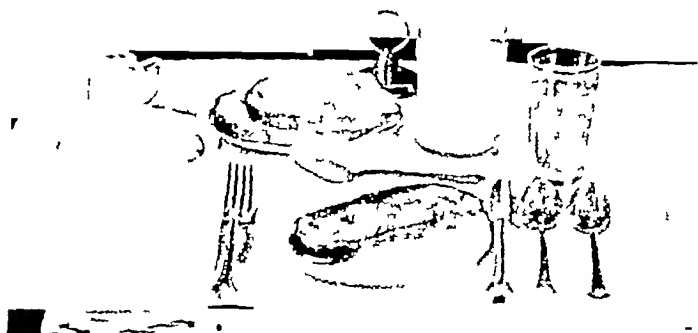


Fig 92 —The above meal consists of banana, orange juice, milk, two slices of bread, cereal and 2 tablespoonfuls of cream

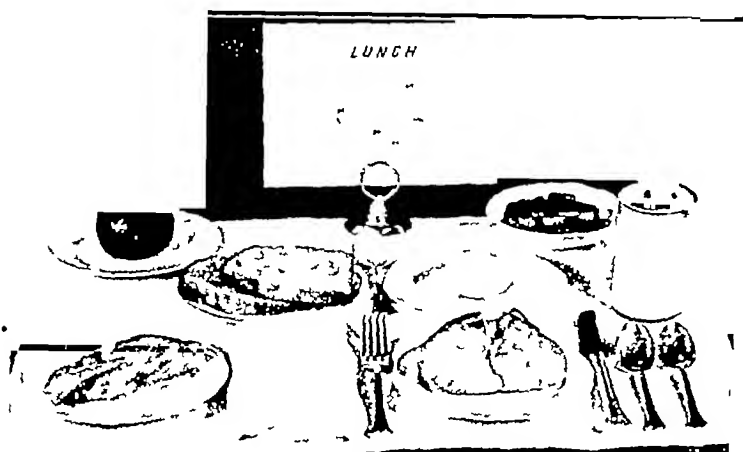


Fig 93 —The above meal consists of baked potato, egg, milk, carrots, two slices of bread, lettuce and an apple

milk are given so that she can include it in the dietary calculation To the carbohydrates thus chosen, meats, fish, eggs, cheese and butter are then added in the units advised until the prescription in respect to the protein, fat, and carbohydrate is filled

The following photographs show the patient's actual choices, and, an analysis of these foods, using the values in the text, will produce figures which approximate the prescription

No matter how simple the preparation of a diet is, one must not expect too much from the patient. The physician who treats diabetes must familiarize himself with food values of many standard objects of diet. In cases where the patient finds difficulty in the preparation of his diet, the physician

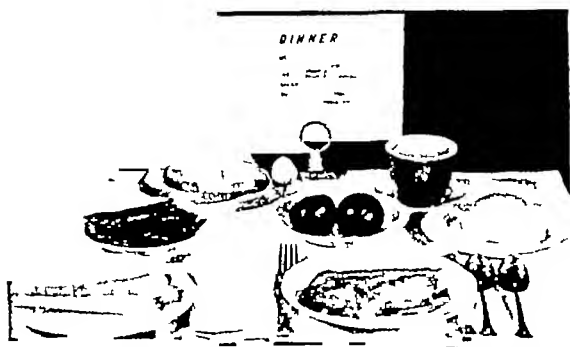


Fig. 94—The above meal consists of roast beef potato string beans, two slices of bread beets, celery and custard

must determine what the dietary needs are and translate them into directions which the patient can easily follow

The majority of cases can be controlled without much trouble, but on the other hand, not all of our patients do as well as the one presented. In the occasional case much experimentation is necessary to maintain the patient in a good state of health, keep him satisfied and yet have laboratory evidence of improvement. These cases are real problems and are a source of much concern as almost every measure affords little help. Their status is either insulin shock or a continued

glycosuria Such patients are followed at more frequent intervals, and the diet and insulin often altered, hoping to strike a balance Fortunately, cases of this type are infrequent It is to be emphasized, however, that their management at the outset in no way differs from the method presented

### SUMMARY

From a review of the literature, ample clinical and experimental evidence has been presented to show that the use of liberal carbohydrate rations in the treatment of diabetes mellitus, is a sound procedure It was emphasized, however, that the most satisfactory results were obtained when, simultaneously with the liberal carbohydrate portions, the fat content, and the total calories were kept relatively low, a plan approaching the principle of undernutrition This method of therapy has proved satisfactory, in our experience Good results from the use of the régime have been reported from other clinics also The preparation of a high carbohydrate-low diet was presented in detail with directions simplified so that the patient, with only slight help from his physician, can prepare his meals with a fairly good approximation to the respective amounts of protein, fat, and carbohydrate prescribed

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## CLINIC OF DR THOMAS T MACKIE

### FIFTH AVENUE HOSPITAL

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#### THE TREATMENT OF INTESTINAL AMEBIASIS

Discussion of the treatment of intestinal amebiasis must distinguish sharply between clinical cure, or the relief of symptoms, and protozoologic cure or complete eradication of the parasites. The one is relatively easy to accomplish, the other often extremely difficult. An adequate therapeutic régime must have the achievement of both goals as its objective. The patient must be protected against recurrence of symptoms and the development of complications, and he must be prevented from becoming a potential source of infection to others. Person to person infection may occur within the family group despite conditions of hygiene and sanitation that are usually considered satisfactory.<sup>1</sup> Complete elimination of the parasites constitutes the essential problem. This requires familiarity with the diverse symptomatology of amebiasis. It necessitates specialized training and knowledge of the biological characteristics of the *Endamoeba histolytica*. It requires familiarity with the pathology in the intestine. And it demands knowledge of the site and mode of action of the many drugs which have been recommended for therapy. Failure to appreciate these essentials and inadequate study of the pathologic problem presented by the individual case are undoubtedly responsible for many of the therapeutic failures.

Few important diseases are so beclouded by misinformation and misapprehension. Standard nomenclature has designated one of the less common clinical phenomena, dysentery, as the generic term for this infection. The characteristic

acute dysentery of the texts is seen much less often than the milder forms of the disease which are unaccompanied by pathognomonic symptoms or physical signs. Until recently it has been considered a purely tropical and subtropical condition. Amebiasis is now known to be widely distributed and to affect from 5 to 10 per cent of the population of the United States. Its distribution is not restricted by climate but by the efficiency of sanitation. Unlike other infectious diseases, the more acute the symptoms the less is the risk of transmission. The chronic cyst passer is responsible for dissemination of the infection.

### SYMPTOMATOLOGY

The symptomatology of intestinal amebiasis is extremely variable and may closely simulate that of many other intra-abdominal conditions. The reaction of a particular patient may be trivial and the diagnosis totally unsuspected until careful stool examinations reveal the nature of the condition. There are many individuals who appear to harbor the infection for long periods of time with little or no clinical evidence of disease. This has led some observers to believe that the *Endamoeba histolytica* may reside in the intestinal tract as a harmless commensal. They question the necessity for protozoologic cure. This view is not generally accepted, however. Acute dysentery, amebic hepatitis, or abscess of the liver may occur at any time when the host-parasite equilibrium is disturbed. The amebae always destroy the tissues of the host even though this may not be clinically evident.<sup>2</sup>

### PATHOLOGY

The pathology of asymptomatic intestinal amebiasis and of acute amebic dysentery differ only in degree and extent. Ulceration is the characteristic process. The lesions are restricted to the colon except in rare instances when the ileocecal valve and adjacent ileum may be involved by extension of an acute process in the cecum. The lesions may occur throughout the colon, or they may be limited to certain areas

The commonest sites in the order of frequency are the cecum, ascending colon, rectum, sigmoid, and appendix. When the ulceration is localized the cecum and ascending colon are much more frequently affected than the rectum or sigmoid<sup>3</sup>. This fact is fundamentally important since cases with localized ulceration do not have dysentery, and may not have diarrhea.

Superficial destruction of the mucosa without appreciable invasion of the deeper tissues constitutes the initial lesion<sup>4</sup>. This may be limited to small areas or it may occur over a considerable extent of the mucous membrane. On gross inspection these changes may be barely discernible. Congestion and thrombosis of minute vascular radicles occurs beneath these areas. The process is usually progressive and ultimately the amebae penetrate into the submucosa and lead to ulceration.

At other times the initial effect appears to be exerted in the depths of the intestinal glands. The amebae pass through the muscularis mucosae into the submucosa. Round cell infiltration, congestion and vascular thrombosis result. The affected tissue breaks down producing a minute abscess cavity. This extends peripherally and ultimately ruptures into the lumen of the colon producing the typical flask ulcer. It presents a small opening, a narrow neck, and a cavity extending laterally beneath the overhanging intact mucosa. The amebae in the abscess wall progressively invade adjacent tissue. Secondary necrosis and sloughing of the overlying mucous membrane occurs producing large areas of ulceration. Although the muscular layers of the intestinal wall offer a relatively effective barrier, the infection may penetrate to the serous coat and lead to perforation.

In the course of such invasion of the tissues the amebae may gain access to radicles of the portal system and be carried to the liver to produce hepatitis or abscess.

#### TREATMENT

Rational therapy must be based upon an appreciation of these fundamentals of the pathology. The essence of the



problem lies in the necessity for simultaneous exposure of all amebae to lethal concentrations of an actively amebicidal drug. Since the parasites are to be found in the lumen of the intestine, on the surface of the mucosa, and within the tissues, the ideal antiamebic drug must fulfill two requirements. It must remain in solution throughout the colon in sufficient concentration to be effective against the organisms in the lumen and on the surface of the mucosa. It must also be absorbed and distributed by the body fluids in a concentration adequate to destroy the amebae lying within the tissues. The many preparations which have been put forward and the equally numerous therapeutic failures indicate that no such ideal agent is available as yet. An effective plan of treatment, therefore, necessitates selection of different drugs to meet varying conditions, and the combination of various preparations to meet the individual requirements of the particular case. There is no universally applicable plan of therapy.

The drugs of recognized value in the treatment of intestinal amebiasis fall into four groups. The alkaloid of ipecac, emetine, organic arsenicals, oxyquinoline derivatives, and compounds of bismuth. All of these have their uses. Many of them have very real and not generally appreciated dangers. Certain ones are definitely contraindicated in particular cases.

**Emetine**—Emetine is probably the most widely known of these drugs. It has acquired an undeserved reputation as an efficient therapeutic agent. It has escaped a well-merited repute for severe and dangerous toxic effects. Although there is no drug which will so rapidly control acute dysentery, Craig<sup>5</sup> has reported that 85 per cent of his cases treated by emetine alone showed persistent infection. Its action appears to be principally upon the organisms within the tissues. Dobell<sup>6</sup> found that the dosage required to rid naturally infected monkeys of their amebae was followed by toxic symptoms in 80 per cent of the animals treated.

The drug is excreted in part by the intestine and in part by the kidneys. Excretion is slow, continuing for days or even weeks. Emetine exerts its major toxic effect upon cardiac

muscle Laboratory animals given from 10 to 25 mg per kilogram of body weight show myocardial degeneration and necrosis followed by scarring<sup>7</sup> Clinically this is expressed by cardiac failure presaged by a rising pulse rate, falling blood pressure, and widening of the cardiac diameters In certain instances a peripheral neuritis resembling that of beriberi results from emetine poisoning

The hydrochloride is the preparation commonly used It should be given deeply intramuscularly and not subcutaneously Intravenous injection may be attended by nausea and vomiting Most authorities believe that harmful effects may follow upon smaller dosage when the drug is administered by this route and that its therapeutic effects are not augmented Individual doses should never exceed 1 mg per kilogram of body weight These are given daily for seven to ten days but the total amount of emetine administered must not exceed 10 mg per kilogram of body weight The majority of the cases of emetine poisoning result from too large individual doses, too prolonged administration, or too brief an interval between courses of treatment The slow excretion of the drug renders it particularly liable to produce cumulative or delayed toxic effects Because of this factor a second course of emetine should not be given until after the lapse of at least six to eight weeks

Two compounds of emetine have been considerably used They have few advantages and some definite disadvantages Emetine bismuthous iodide is administered by mouth It frequently causes severe nausea and vomiting It is not a specific cure and its therapeutic efficiency is such as seldom to justify the trials and discomforts attendant upon its use The periodide of emetine is better tolerated but seems to be a less efficient amebicide than the bismuthous iodide Both of these preparations may lead to emetine poisoning

**Arsenicals**—Various organic arsenicals have been used in the treatment of amebiasis Like emetine, however, they are not completely efficient, and they are not free from harmful effects upon certain patients

Stovarsol (acetarsone) has gradually fallen into disrepute. It contains 27.2 per cent of arsenic which is slowly and irregularly excreted. It has been a frequent cause of arsenic poisoning. Approximately one of every six patients taking the drug in the dosage usually advised shows evidence of intolerance to it. This may occur suddenly and without warning, producing fever, dermatitis, liver damage, and visual and acoustic disturbances. The therapeutic value does not balance the hazard of intoxication and in consequence it has no justifiable place in the treatment of amebiasis. The same may be said of treparsol.

Recently another organic arsenical, carbarsone, has been produced. Although it contains 28.85 per cent of arsenic it is said to be definitely less toxic than stovarsol and more actively amebicidal in tolerated doses.<sup>8</sup> It is absorbed from the gastro-intestinal tract and excreted in the urine. Anderson and Reed<sup>7</sup> report that 90 per cent of their cases have responded satisfactorily to the oral administration of this drug. For the average adult they recommend 0.25 Gm twice daily for ten days. It may be given rectally, as well, in the form of a 2 per cent retention enema.

**Oxyquinoline**—Oxyquinoline derivatives have been widely used. They are marketed under a variety of trade names and include yatren, quinoxyl, anayodin, and chiniofon N N R. They contain approximately 28 per cent of iodine which is excreted in the urine. These preparations have little if any toxicity. They are somewhat irritating to the intestinal tract in some individuals increasing or producing diarrhea. This can usually be controlled, however, without difficulty and seldom necessitates withdrawal of the drug.

These preparations are supplied as enteric coated pills each of 0.25 Gm. The dosage is from two to four pills three times daily before meals for eight to ten days. They may also be used in 1 per cent to 2.5 per cent solution for retention enemata. The solution, however, should be freshly prepared and not heated since this leads to decomposition of the drug.

O'Connor and Hulse<sup>9</sup> using anayodin reported only 2 ther-

apeutic failures among 51 cases of amebiasis who were followed for periods of six months to two years. The drug appears to exert a direct action only on the parasites in the intestinal tract and is ineffective for liver abscess. The writer also has found this preparation of value<sup>10</sup> although relapses have occurred somewhat more frequently. In cases of acute dysentery recognizable trophozoites of *Endamoeba histolytica* were not demonstrable after the second day of oral treatment.

A somewhat similar compound, iodochloroxyquinoline (Vioform N.N.R.) has received favorable comment<sup>11</sup>. It contains about 40 per cent of iodine and about 12 per cent of chlorine. It is said to be less toxic and more effective in smaller dosage in monkey amebiasis than the other oxyquinoline preparations. Animals killed by a large single dose, however, show some degree of liver necrosis. The drug is absorbed from the gastro-intestinal tract to some extent, and excreted in the urine. It is supplied in capsules containing 0.25 Gm each and is usually given in two courses of 0.75 Gm daily for ten days with a week's rest between. This compound is irritating to the rectal mucosa and should not be used for retention enemata.

**Bismuth**—James and Deeks<sup>12</sup> obtained good results from massive and long-continued dosage of bismuth subnitrate. Nitrate poisoning may follow upon overdosage. This hazard and the relatively low amebicidal activity of bismuth compounds have not entitled it to an important place among the antiamebic drugs. The less toxic subcarbonate, however, is useful in the symptomatic control of diarrhea in acute dysentery.

#### DISCUSSION

It is apparent that the therapeutic plan for the individual case must be based upon evaluation of the intestinal pathology, upon the site of action and the side effects of the various drugs, and upon associated disease states. The latter not infrequently constitute positive contraindications to the use of certain of these preparations. In the presence of cardiac

disease emetine must be used with extreme caution if at all, and then only under the closest observation. The various preparations of arsenic are hazardous to a patient with liver or renal damage. The plan for the uncomplicated case must be based upon the character and severity of the symptoms and the probable severity and extent of the ulceration.

A patient with acute dysentery should be confined to bed during the period of treatment and thereafter until such time as proctoscopic examination and the character of the stool indicate that the lesions have largely or entirely healed. The certain presence of amebae within the tissues of the colon where they are relatively inaccessible to drugs active in the intestinal contents, requires the use of emetine when not definitely contraindicated. It should be used with strict attention to the theoretical toxic threshold. Although this drug alone will not infrequently check an acute dysentery abruptly, the relief of symptoms must not be accepted as evidence of cure. The organisms in the more superficial lesions must be attacked at the same time by the exhibition of carbarsone or one of the oxyquinoline preparations given by mouth and by retention enemata. For the more acute cases opium may be required to control pain, cramps, and tenesmus. Bismuth subcarbonate is useful in certain instances to alleviate a severe diarrhea in the early stages of treatment. Throughout the period of active ulceration and healing the diet should be soft and free from irritating and undigestible residue.

The milder cases of dysentery and of amebic diarrhea are best treated in similar fashion although if there is little or no evidence of extensive ulceration on abdominal examination and by proctoscopy strict confinement to bed may be unnecessary. It is unwise, however, to use emetine in full therapeutic dosage for ambulatory patients. Following the use of this drug the patient should be cautioned against strenuous physical exertion for a period of several weeks.

The chronic cyst passer who is relatively asymptomatic presents a different problem. Although ulceration of the colon is unquestionably present, these individuals frequently respond

to less exacting treatment. One or two courses of oral therapy by one of the oxyquinoline preparations or by carbarsone may be sufficient to eliminate the infection. This does not necessitate curtailment of the patient's activities. However, if cysts continue to be present in the stools after repeated courses of these drugs it is the writer's practice to resort to the intensive treatment used for acute dysentery. This seldom fails to eradicate the infection.

The accomplishment of protozoologic cure constitutes an essential part of the proper management of the individual case. It is difficult to achieve because the average practitioner is unfamiliar with the detailed biology of the *Endamoeba histolytica* and lacks the specialized training in protozoology necessary for complete study of the patient. Many infections pass unrecognized on this account. James<sup>18</sup> has said "Nearly twenty years of work on this subject has convinced me, and, I may add, others better qualified than myself, that the correct diagnosis in fresh material of intestinal amebiasis not associated with dysentery, and the proper identification of the four species of amebae commonly found in the stools, is a task requiring long and special training, and is not to be entrusted, as it so often is, to the ordinary worker in the laboratory or the inexperienced technician." Following treatment, the patient must be kept under observation for eighteen to twenty-four months. During this period careful stool examination must be made on three or four consecutive days every two or three months since the encysted forms may be present in the stool only irregularly. The patient may be assured of complete cure only after such a follow-up period during which there has been no indication of persistent infection.

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## CONTRIBUTION BY DRS DOUGLAS SYMMERS AND KENNETH M LEWIS

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### THE ANTITOXIN TREATMENT OF ERYSIPELAS, WITH OBSERVATIONS ON 4698 PATIENTS SO TREATED

UNTIL Birkhaug, in 1926, obtained a specific toxin from the hemolytic streptococcus of erysipelas and showed that in turn it could be neutralized by an antitoxin, the treatment of erysipelas had been on an unscientific basis. Attention was focused on the rash, and local remedies were legion. It was established that none of the ointments, lotions, irritants or dyes had the least effect in controlling the disease. The fact that erysipelas is a constitutional disease, that it is caused by a specific micro-organism and that the rash is a local manifestation seemed to be lost sight of even after the science of bacteriology had been founded.

In May, 1927, we began to employ an unconcentrated antitoxin furnished to us gratuitously by the Lederle Laboratories of New York. With the use of this antitoxin we obtained results that could not fail to impress us. Patients with a rapidly spreading rash and a temperature of 104° to 105° F would show fading of the rash and decline of temperature to normal in from one to three days. The following year a concentrated antitoxin was used and this has been continued to date.

In September, 1927, a preliminary report on 131 patients so treated was criticized on the basis that the severity of erysipelas varies from year to year and the opinion was expressed that possibly the year on which we were reporting



was a mild one. A year later further observations were reported and again in 1932, after five full years with this method of treatment, we found that the clinical observations and the figures for mortality and duration had been reduced in the same manner as shown in the preliminary report. At the present time we are bringing our period of observation up to May, 1934, a total of seven years.

We strongly recommend using the antitoxin intramuscularly and not intravenously, since our results with the intramuscular route have been satisfactory, and we have experienced several severe reactions from using it intravenously. We administer 10 cc of the concentrated antitoxin intramuscularly as soon as the patient is admitted to the hospital and we repeat this dose every eighteen to twenty-four hours, depending on the severity of the disease, until the desired effect is obtained. If, after six injections, there is no improvement, we discontinue the use of the antitoxin. Our criteria for judging the effect of the medication are fall in temperature and fading of the rash which also ceases to spread. We use the same dosage and frequency in children as in adults. During the past year 75 patients were treated with 20 cc doses of the concentrated serum, hoping to improve results. We found, however, that the results remained the same as in the group receiving 10 cc.

With this method there are two points that should be borne in mind. First, the antitoxin should be administered as soon as the diagnosis is made and it should be repeated at eighteen to twenty-four hour intervals for a maximum of six doses, unless the disease has been arrested in the meantime. In every condition in which an antitoxin or serum is of value, the earlier treatment is started the better are the results. We have seen a number of failures in which it was felt that procrastination in using the antitoxin was the cause. These patients are so saturated with erysipelas toxin that no matter how much serum is given, it is impossible to overcome the toxemia. In cases, in which the diagnosis is indefinite, lying between so-called "cellulitis" and erysipelas, we are in favor

of administering antitoxin. If the case proves to be the former, no harm is done, but if it should prove to be the latter, much is gained by the institution of early treatment.

Second, as mentioned above, we advise the intramuscular route, since we have noted severe reactions from intravenous administration.

There are numerous factors, which in our opinion, are responsible for the fact that a certain number of all patients with erysipelas do not respond to the antitoxin method of treatment, for example, delay in administration of the antitoxin at the onset and failure to repeat adequate doses at appropriate intervals are reasons for not obtaining good results. It is surprising to note that patients are not infrequently allowed to go for two or three days before the use of antitoxin is initiated and in whom, even when treatment is started, injections are not repeated frequently enough. Other factors that effect the result are the age and general condition of the patient. In infants and children and in the aged, erysipelas is a serious disease and the mortality is high. Alcoholics and the otherwise drug debauched and the debilitated are, needless to say, individuals with lowered resistance and in them the disease is of more serious moment than in the vigorous and the temperate.

An important factor in the group of resistant patients is that the streptococcus of erysipelas is a micro-organism of different strains. In preparing the antitoxin an attempt is made to incorporate as many representative strains as possible. If, however, in a patient in whom the offending streptococcus happens to be of a strain not contained in the serum, it is evident that the result in that particular patient is not apt to be satisfactory.

It has been our custom to divide erysipelas into two types, namely, the facial and the body type. The facial type is usually limited to the face, neck and head, is the less severe of the two and responds more readily to treatment. The body type is more severe and less responsive to treatment. We feel that abrasions on the skin or operation wounds are not

essential to the development of the disease. In by far the greater number of patients, there is no detectable break in the skin and the rash occurs in apparently normal areas.

From five to ten days following the use of the serum, serum sickness may occur. This is characterized by rise in temperature, local or generalized urticaria, often with intense itching, rapid pulse and sometimes arthralgia. Serum sickness is not a serious condition and is apt to subside in about forty-eight hours. If the attack is severe, relief may be obtained by the use of 5 to 10 minims of adrenalin solution 1-1000, given subcutaneously and repeated at frequent intervals.

We have found that there are approximately five out of every hundred patients in whom erysipelas antitoxin is of no value. These patients must be classed in a group whose infection is caused by a strain of the micro-organism not used in the preparation of the serum, and, furthermore, it is to be emphasized that the use of erysipelas antitoxin does not protect against further attacks.

Among the complications of this disease, the most important is the formation of abscesses, usually under that area of the skin over which the rash has passed. These subcutaneous collections of pus should be treated by surgical incision and adequate drainage. They are apt to occur in the second and third week following the onset of the attack and are associated with rise in temperature and usually with redness and fluctuation. We have found that this condition occurred with greater frequency and the abscesses were of greater extent in the years before the use of antitoxin.

In analyzing our results from May, 1927, to May, 1934, there was a total of 4698 patients treated in the erysipelas wards at Bellevue Hospital. Of this number there were 2605 men, 1575 women, and 518 children. In 1928 a study was made of the duration of the disease in each patient treated with antitoxin as compared with a similar group treated the previous year with local remedies. It was found that the average duration of the disease had been reduced by 60 per cent in the group treated with serum. This reduction was

based upon the total number of days of hospitalization. From 1904 to 1926 there were 15,277 erysipelas patients treated at Bellevue Hospital without antitoxin. There were 1543 deaths, a mortality of 10.1 per cent. From May, 1927, to May, 1934, 4698 patients were treated with antitoxin. There were 340 deaths, an average mortality of 7.2 per cent, or a total reduction of approximately 30 per cent in the number of deaths.

COMPARATIVE MORTALITY STATISTICS, ALL AGES  
WITH ANTITOXIN AND WITHOUT ANTITOXIN

	Number of patients.	Deaths.	Mortality rate per cent.
With antitoxin May 1927 to May 1934	4 698	340	7.2
Without antitoxin 1904 to 1927	15,277	1543	10.1

COMPARATIVE MORTALITY STATISTICS OF INFANTS (BIRTH TO TWO YEARS) AND  
ADULTS WITH ANTITOXIN (MAY 1932 TO MAY 1934) AND WITHOUT ANTI-  
TOXIN (MAY 1925 TO MAY 1927)

Infants

	Number of patients.	Deaths.	Mortality rate per cent.
With antitoxin	100	14	14
Without antitoxin	80	30	47.5

Adults

	Number of patients.	Deaths.	Mortality rate per cent.
With antitoxin	1189	83	6.9
Without antitoxin	891	82	9.2

We have studied the results of a separate series of infants and adults over two periods of two years each, one from May 1, 1925, to May 1, 1927, when antitoxin was not used and the

treatment consisted of local remedies only, and the second from May 1, 1932, to May 1, 1934, when antitoxin was used as a routine measure. We have incorporated these findings in the accompanying table where it is to be noted that the mortality rate in 100 infants was reduced from 47.5 per cent to 14 per cent. In the adult group there were 1189 patients treated with antitoxin with a mortality of 6.9 per cent, and in 891 patients treated without antitoxin the mortality was 9.2 per cent. Particularly to be observed is the improved results in infants. Any method of treatment which so lowers the mortality rate in a group in which the number of deaths was previously excessive, should be considered of value.

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### THE MANAGEMENT OF ACUTE, CHRONIC, AND TER- MINAL BRIGHT'S DISEASE

SPECIFIC therapy is lacking, the management of Bright's disease therefore is a problem of supporting the natural resistance and recuperative powers of the patient.

The chief object in the treatment of acute nephritis is to prevent the disease from becoming chronic. When the chronic condition has become established there is little hope of preventing its eventual progress. The object of therapy then becomes the prevention of exacerbation of edema, and other complications. It is often possible thus to maintain the patient in a state of comparative well being and activity until renal function has fallen below one tenth of the normal value.

Acute nephritis is in many cases an after-effect of streptococcus infection. Unless the nephritis becomes chronic recovery is usually complete or well on its way within four to six months. There is as yet no means of predicting whether the patient will be cured or pass into the chronic phase of the disease. In general those patients in whom the onset is sudden and stormy with gross hematuria, have a better prognosis than those in whom the onset is insidious with edema and scant hematuria. The reason for this is not known.

It must be recognized that diffuse nephritis does not usually exhibit the characteristics of a direct bacterial infection but more those of sensitization. The disease manifests itself late in the course of an infection, seldom at its incep-

ency It seems desirable to manage the patient with acute nephritis as though he were suffering from an infection Unfortunately, it is a manifest impossibility to put the kidneys at rest If fluids are not administered the kidneys work against great osmotic tension to elaborate a concentrated urine Conversely, administration of large amounts of fluid adds to the edema and work of the heart

### ACUTE NEPHRITIS

**General Management**—Particular care must be taken to ascertain whether the patient has been poisoned with mercury, lead or salvarsan Treatment may be specific provided the noxious agent is discovered

Complete rest in bed is required throughout the course of acute nephritis The patient must also be protected from chilling by use of light flannel garments Tub baths had best be omitted Cleanliness may be maintained by warm sponges followed by an alcohol rub Mineral oil (16 cc b i d) with psyllium seed (2 teaspoonfuls in water) will regulate the bowels, without purgation

The patient is not allowed out of bed until there are definite signs, either that the disease has progressed into the chronic stage, or that healing has taken place In general a cure may be determined by subsidence of edema, falling of the blood pressure to normal, disappearance of red blood cells and albumin from the urine, return of appetite and rise to normal of renal function (urea clearance or ability of the kidneys to concentrate) Most patients are allowed to leave their beds much too early The so-called "healed patient" should be watched more carefully than the "healed syphilitic" throughout his life

**Diet**—Ordinarily the very acute phase of nephritis does not last long enough to cause serious loss of weight The caloric intake may therefore be disregarded

In occasional cases, apparently much more rare in this country than Europe, cardiac dilatation and failure occur during the first days of acute nephritis If cardiac signs oc-

cur, the case is treated as one of threatened heart failure, with strictest bed rest, digitalis, and with no food or fluids except a glass of orange juice or glucose lemonade three times a day. This régime is followed for four or five days, a more liberal diet is then resumed. Both Volhard in Germany, and Ellis in England, employ a preliminary starvation period during the treatment of acute nephritis. Volhard allows the patient no food or fluids for from three to five days, following which a large volume of water (1500 cc.) is given at one time. Ellis, on the other hand, allows a pint of orange juice, in 6 portions, each twenty four hours, and often continues this diet from ten to fourteen days if the blood pressure has not returned to normal.

In cases without cardiac symptoms, not acutely ill, and free from edema, the usual hospital diet is permissible throughout the attack, in so far as the subject's digestive and general condition permits. The diet should be balanced and preferably adequate with respect to calories, proteins, and vitamins, to maintain a state of good nutrition. No specific restriction of either protein or water is indicated. If edema is present, salt intake is restricted.

**Edema.**—Edema occurring during Bright's disease is of three kinds. *Initial edema*, usually seen during the first days of the acute stage is apparently due to increased permeability of the capillaries. It lasts rarely more than two to four weeks and requires no treatment. It may rapidly give way to the *nephrotic* type of edema which is due to depletion of the plasma proteins. Reduction of plasma protein to the level, about 5 per cent, at which edema forms, may occur within the first month of the disease. Ordinarily, the initial edema first disappears to be followed later by the appearance of the nephrotic type provided the disease has progressed to the chronic active stage and loss of protein is occurring in the urine. The third type, *cardiac edema*, is seldom observed in this country during the acute stage of nephritis. It is due to increase in capillary pressure and is not caused by reduced level of plasma proteins.



If edema persists after the first fortnight, it is usually attributable to a fall in plasma protein content, the diet in such cases is planned to rebuild plasma and tissue proteins, and is administered as described below for chronic cases with edema. Food restriction, other than salt deprivation in edema, need be practiced only when clinical observation indicates that the patient's reaction to the diet is unfavorable.

**Anuria**—Urinary suppression is fortunately rarely observed as a symptom of acute nephritis. No therapeutic procedure has been sufficiently carefully evaluated to be certain that it will yield beneficial results. The patient should first be catheterized to make certain that there is no obstruction to the flow of urine.

It is advisable to administer full therapeutic doses of digitalis. Hypertonic glucose solution (50 per cent) should be given intravenously. Occasionally diuresis is thus started. Certain observers have noted remarkable results from the withdrawal of from 300–400 cc of blood. Warm baths lasting from one to one and one-half hours may be useful during the first day or two of anuria. Acidosis is combated by administration of alkali by rectum or by vein (see p 880) and sodium chloride if the chlorides in the plasma are low.

Should these measures fail, decapsulation should be considered. Opinion differs greatly as to the value of the procedure, but many observers have seen beneficial results (Edebols, Volhard). The operation can be performed under local anesthesia if necessary. It does not appear necessary to operate on both kidneys. The operation in itself need not be dangerous. If it is to be performed it should be done not later and preferably earlier than the third day of anuria.

Radiation with x-ray has been highly recommended by Stephen. He administers  $\frac{1}{6}$  to  $\frac{1}{4}$  skin erythema dose over each kidney.

If the anuria were in fact due to overirritability of the renal nerves, spinal anesthesia might be of value in causing relaxation of the constricted blood vessels. The author has observed but one case in which this treatment was given. The

results were not encouraging though it must be admitted that the treatment was given on the fourth day of anuria

**Medicinal Treatment**—Cardiac complications are treated in the usual manner with digitalis given by mouth. It is fortunate that such complications are rarely seen in this country. Venesection need but seldom be employed except when convulsions or other evidence of hypertensive encephalopathy, as described by Fishberg, occur. Should anuria supervene 300–400 cc of blood should be drawn. Vomiting is often a serious and distressing symptom. If enemata and withdrawal of food and fluids do not suffice to put an end to it, four doses of 6 drops of 1 per cent cocaine in  $\frac{1}{4}$  glass of water every half hour may be of use. This failing, hypertonic glucose may be given by vein.

Convulsions during acute nephritis are rare in our experience. Chloral hydrate (1.5 Gm. three times daily) aids in preventing their onset. Hypertonic glucose given by vein is of especial value in their treatment. Magnesium sulphate administered intramuscularly is rarely indicated. The dose may be 0.3 cc of a 25 per cent solution for every kilogram of body weight given intramuscularly. This may be repeated in four hours.

Pain over the lumbar region may be combated with mustard or belladonna plasters, hot water bottles, or heating lamp. Some patients find Baume Bengue soothing, most do not. Chloroform liniment is but temporarily effective.

**Surgery**—Elective surgical procedures should under no circumstances be undertaken during the course of acute nephritis. This rule is well substantiated by experience. Most infectious foci should be conservatively handled until recovery is sufficient to obviate the danger of abetting the morbid process in the vascular system by surgical operation.

**Physiotherapy**—Critical evidence indicates that known physiotherapeutic measures such as diathermy are of questionable value in the management of acute nephritis. Baths and vigorous massage may be harmful.

## CHRONIC NEPHRITIS

**General Management**—Management of chronic nephritis should be so directed that exacerbations are avoided, and the patient enjoys life as nearly to its end as is possible

Exposure to chilling and infection must be avoided to the utmost ability of the patient. The possibility of chilling may be offset by wearing light woolen underwear and interdicting sea bathing. Sunburn may be dangerous to chronic nephritics. Tepid baths followed by gentle massage should be a regular part of the daily routine.

Exercise of a moderate nature is to be encouraged. Indeed the "good life" should enlist the chronic nephritic. Moderation but not abstemiousness should be his guide.

If slight noncardiac edema does not clear up during a few weeks of bed rest and diet, it may be desirable to allow the patient up and about his duties for a trial period. At times edema will disappear without apparent provocation.

The bowels may be controlled by the use of stewed fruits and a sufficiently bulky diet. Psyllium seeds and mineral oil may assist. Seldom are the more drastic purgatives necessary. Effervescent magnesium citrate is perhaps one of the least offensive of these.

Mail order houses and laboratories of the corner drug store often become foci of hypochondria. Urine analysis should be restricted to those performed by the physician in charge. One glance at the printed "interpretation" of the analysis issued by business concerns must convince the patient how lugubrious is his fate. This hardly aids the physician in his effort to keep the full confidence of the sufferer.

**Diet**—Until recent years the customary diet prescribed in chronic nephritis has been low in proteins. The low protein diet has been founded on two assumptions. The first is that minimizing the excretion of nitrogenous products, especially urea, would rest the kidney and retard its rate of destruction. The second assumption is that lowering the dietary protein tends to lower elevated blood pressure. Neither of these

assumptions has ever been proved, and both are contrary to modern observation carried out on controlled cases over long periods

On the other hand, the low protein régime neglects the need of many patients for *a diet more than ordinarily rich in proteins*. The rapid loss of protein in the urine in either nephrosis or the intermediate chronic stage of glomerular nephritis causes a protein deficit in the plasma. This deficit has been shown beyond doubt, both by clinical observation and experiment, to cause the type of noncardiac, "hydremic" edema which is characteristic of these conditions. The tendency to this edema begins to be marked as a rule when the plasma protein content, normally 7 per cent, falls below 5. Furthermore, the protein loss is usually accompanied by wasting of the tissues, which apparently are sacrificed to provide material for replacement of the excreted plasma proteins. In consequence the patient, beneath his layer of edema, is emaciated and weakened. He is also peculiarly susceptible to infection. The hydremic syndrome, with its edema and weakness, more frequently than any other element of the disease, turns the patient into a bedridden invalid. If the protein content of the plasma and tissues can be maintained, most nephritics can be kept relatively symptom free and active until the terminal stage of the disease approaches.

It is, therefore, often desirable to feed protein liberally in order to replace, in so far as possible, that which is lost from both tissues and plasma. The change from low to high protein diets may improve rather than depress renal function. It is essential to allow sufficient carbohydrate and fat in order that the patient may be enabled to utilize the protein for plasma and tissue reconstruction rather than for energy production. Ordinarily, 100 Gm. of protein is sufficient for a diet yielding 2200 calories. Some patients may require as high as 125 to 150 Gm. of protein which is about the maximum that can be taken. Most patients prefer much of the protein as meat, but others find this burdensome. An easy method of administer

ing protein is by use of edible casein,<sup>1</sup> in doses of 20 to 30 Gm in a glass of milk. It is tasteless and ordinarily well tolerated.

*Effects of Dietary Protein, Salt, and Water Intake on Edema*—High protein diets may yield dramatic results in those patients who have, previous to the diet, been systematically protein starved. In those who have adhered to normal dining habits and yet developed edema the results may prove anything but hopeful. In some cases, with heavy urinary protein loss or poor regenerating ability, even diets with 125 to 150 Gm of protein, may fail to raise the plasma protein and alleviate the edema. However, even prolonged failure should not discourage continuance of high protein diets, as the plasma proteins may eventually rise and edema disappear.

When no edema or tissue wasting is present and not more than 1 to 2 Gm of protein daily are being lost in the urine, there is no reason for prescribing more than the ordinary amount of protein (60 to 80 Gm) in the diet.

During the more advanced stage of nephritis, edema often disappears and albuminuria diminishes without treatment. No advantage can be expected from feeding such patients a high protein diet, on the other hand, malnutrition should not be induced by unnecessary protein restriction. The diet should be normally balanced with regard to fat, carbohydrate, proteins, minerals, and vitamins, in order to maintain optimum well-being. Regardless of blood urea and nonprotein nitrogen elevation, proteins need be restricted only when they cause subjective discomfort.

There is another tangible and controllable factor besides plasma protein deficit that is important in edema production, this factor is the hydropigenous effect of sodium chloride consumption. Salt must therefore be withdrawn from the diet of patients who have edema or those who because of plasma protein deficit are potentially edematous. Not more than 3 Gm of salt is allowable. Most patients soon become accustomed to this but others prefer the addition of such salt substitutes.

<sup>1</sup>Edible casein F-S 3 of the Casein Manufacturing Co., 350 Madison Avenue, New York.

as Hosal Insipid foods may be flavored by the use of vinegar, lemon juice, or onion Addition of salt to the diet of a patient who has been edema free on a salt poor diet may rapidly cause edema to appear If the diet is very low in salt (below 2 Gm ) it is advisable to be on guard for appearance of hypochloremia, which appears in some cases to be a cause of weakness and malaise, and if accompanied by dehydration may hasten the onset of uremia An occasional determination of chlorides in the serum will aid in avoiding this complication Hypochloremic uremia is especially prone to occur when salt is being washed out of the body by continuous polyuria, and more especially by diarrhea, or vomiting

With regard to fluid intake, the patient may usually best be permitted to follow his own desires, except when cardiac embarrassment occurs In noncardiac edema of the nephritic type, water is retained only with amounts of salt sufficient to form physiologic saline solution with the water Sometimes, in fact, water drinking may encourage excretion of edema fluid by washing out salt It is restriction of salt, and not of water, that is called for

Cardiac edema, in contrast to nephritic edema, is characterized by the absence of plasma protein deficit and the presence of signs of cardiac embarrassment This condition is treated as in cardiac decompensation, and fluid restriction is indicated

**Medicinal Treatment**—Diuretics appear to have limited usefulness in the treatment of chronic nephritis The purine derivatives are ordinarily not effective Salyrgan may start diuresis but must be employed with great caution due to its irritating effect on the kidneys Ammonium chloride in doses of 2 to 3 Gm three times daily does not appear harmful but it must be remembered that it produces acidosis and should be employed only when the alkali reserve is followed by laboratory determinations Diuretics will increase excretion of water, but, as the author has shown, no increase in the ability of the kidneys to excrete waste products such as urea may be expected Intravenous injection of salt free solutions of gum acacia may

initiate diuresis The acacia solution must be prepared from pure gum acacia (30 Gm in 300 cc water) and administered very slowly The quality of the gum is of importance Lack of observance of these precautions will almost surely lead to appearance of a syndrome resembling anaphylactic shock

*Nephritic anemia* is usually not at all influenced by hematincs such as iron or liver If exacerbation of the anemia from other causes, such as hemorrhage, occurs iron in the form of ferum reductum (1 Gm three times daily) may assist in raising the blood hemoglobin back as high as it was before the exacerbation Certain patients complain that the iron causes gastric irritation Small blood transfusions (250 cc) repeated every three weeks sometimes are justifiable Justification often depends on the economic status of the patient

*Cardiac complications* should be anticipated as early as possible and treated in the usual manner with digitalis Nephritic patients do not appear to be either more or less susceptible than others to the action of this drug

Venesection must occasionally be resorted to when the right ventricle of the heart begins to fail The benefit to be attained must be carefully weighed against the disadvantages accruing from further loss of hemoglobin in an already anemic patient We employ it rarely

No known drug will reduce the *hypertension* of these patients for a sufficiently long time to be of any value Nitrites, thiocyanate, bismuth subnitrate, mecholol (acetyl  $\beta$ -methyl cholin) are useless

Lumbar puncture is a procedure which only occasionally produces beneficial results Even though the fluid pressure is increased, removal of fluid is not usually attended with fall in blood pressure level or betterment in the patient's symptoms Indeed, spinal puncture may cause temporary elevation in blood pressure level Possibly the best that can be said for it as a therapeutic measure is that it is not contraindicated

In cases advanced toward uremia, intravenous injection of hypertonic glucose solution often appears to alleviate a protean

group of symptoms ranging from convulsions and uremic twittings to pain in the abdomen and vomiting

Sleep must not be denied the chronic nephritic Chloral hydrate in doses of 1 Gm three times a day, helps to allay a feeling of nervousness of which many patients complain Amytal (0.2 Gm or 3 grains) with a warm drink is useful at night Headache may be controlled with amidopyrine (0.3 Gm or 5 grains) or acetylsalicylic acid Codeine (32 mg or  $\frac{1}{2}$  grain) administered with the headache remedy often gives comfort to the patient Ice-bags and massage over the occiput are useful

Itching may become one of the most obstinate symptoms to be treated Ergotamine tartrate administered orally (0.001 Gm or  $\frac{1}{60}$  grain, three times daily) is said to be useful Obtundia cream<sup>1</sup> has proved its value and should certainly be given a trial Calamine may give temporary relief but is soon rubbed off by the bedclothes

Appetite may be stimulated by port wine (45 cc) taken fifteen minutes before the meal Taken as an hors d'oeuvre it is less useful Gastric flatulence often is aided by the use of creme de menthe administered with cracked ice from a thin large glass

**Surgery**—Removal of infected foci such as teeth and tonsils may be undertaken without undue risk, provided the function of the kidneys is not too much impaired (below 20 per cent normal urea clearance) Occasionally uremia may be precipitated in patients whose function is low by what would be considered a minor surgical procedure Removal of foci should be undertaken for general hygienic purposes It is unlikely that it will influence the course of the nephritis

**Physiotherapy**—Diathermy in the author's experience has proved of no value

Unfortunately the physician is often helpless in preventing the progression of the disease If malnutrition and circulatory failure can be prevented, however, it is often possible by atten

<sup>1</sup> Obtundia cream may be obtained from Oti Clapp and Co., Boston Massachusetts



tion to detail to maintain nephritic patients in a surprisingly good state of well-being until a few weeks, or even days, before the inevitable uremic or circulatory exitus

### UREMIA

Most cases of uremia do not recover. Rarely, however, recovery may be sufficient to permit the patient to live a useful life a year or more before relapse into coma and death. The main effort in the management of uremia is to keep the patient as comfortable as possible. Symptoms are treated as they arise. Diet usually becomes a secondary consideration.

**Diet**—Since nephrotic edema often spontaneously disappears during the terminal stage of nephritis it is not necessary or desirable to force protein in order to keep the plasma protein above the edema level. The greater portion of the diet should consist of fat and carbohydrate with enough protein, if acceptable to the patient, to balance loss through wear and tear of the tissues. Usually from 30 to 50 Gm of protein will suffice. As the patient's appetite is seriously impaired, palatability of the diet ordinarily takes precedence over its chemical composition.

Fluids should be neither restricted nor forced during the course of uremia. Enough fluid and salt must be given to counterbalance the nearly constant output of both and prevent dehydration. Conversely, fluids should not be forced, as this only adds greater strain to an already overtaxed heart. If because of vomiting sufficient fluids cannot be retained they should be given by vein or by rectum.

Salt depletion leads to dehydration. It is, therefore, irrational to restrict salt when dehydration occurs in uremia. On the contrary, physiologic saline (500 to 1000 cc) should be given by vein or under the skin. Glucose (10 per cent) may advantageously be added to the solution. The warm solution should not be administered at a rate greater than 200 cc per hour. Given in this manner cardiac embarrassment but rarely occurs.

Acidosis may or may not accompany uremia. If it occurs,

it adds the dyspnea of acidosis to the distress of the patient. The acidosis can be relieved by administration of alkali, which is given by mouth in repeated doses of 3 to 5 Gm if the patient can take it. Otherwise the bicarbonate must be given by intravenous injection.

By mouth alkali may be given in the form of bicarbonate, citrate, or acetate of sodium. The organic radicles of the citrate and acetate are burned, so in the body these salts are turned into bicarbonate.

For intravenous injection, sodium bicarbonate alone has thus far been ordinarily used. An isotonic solution of it contains 13 Gm per liter. If the solution is first prepared and then sterilized by heat, it turns intensely alkaline from loss of  $\text{CO}_2$ , and the reaction must be restored by running a stream of carbon dioxide through the solution until it is no longer red to phenolphthalein. However, a more convenient way was introduced by Rogers, who sterilized the solid bicarbonate by dry heat in packages, and then dissolved it in sterile water or saline solution.

The amount of bicarbonate required to restore a normal alkali reserve should be calculated from the  $\text{CO}_2$  content of the blood plasma (Palmer and Van Slyke). The rises in plasma  $\text{CO}_2$  and bicarbonate concentrations are approximately what they would be if the bicarbonate were added to a volume of fluid containing 0.7 liter for each kilo of body weight. The amounts required to raise the alkaline reserve to the point indicated by 60 volumes per cent of plasma  $\text{CO}_2$  content, or 25 millimoles of  $\text{BHCO}_3$ , and pH 7.4 are indicated by the line chart on Fig. 95 (Van Slyke).

When injections are given it is well to calculate both the amount of bicarbonate required to restore a normal alkaline reserve and the volume of fluid required to restore that lost from the body as nearly as this can be estimated from the loss in body weight or otherwise. To the volume of isotonic bicarbonate solution required to restore the alkali reserve is added the volume of 0.9 per cent NaCl solution required to make a total volume sufficient to replace the lost body fluids.

When large amounts are required, the infusion is made in portions at suitable time intervals apart

In rare instances where acidosis develops over a period of weeks or months it may be desirable to give a few grams of sodium bicarbonate daily by mouth as an aid to the general comfort of the patient

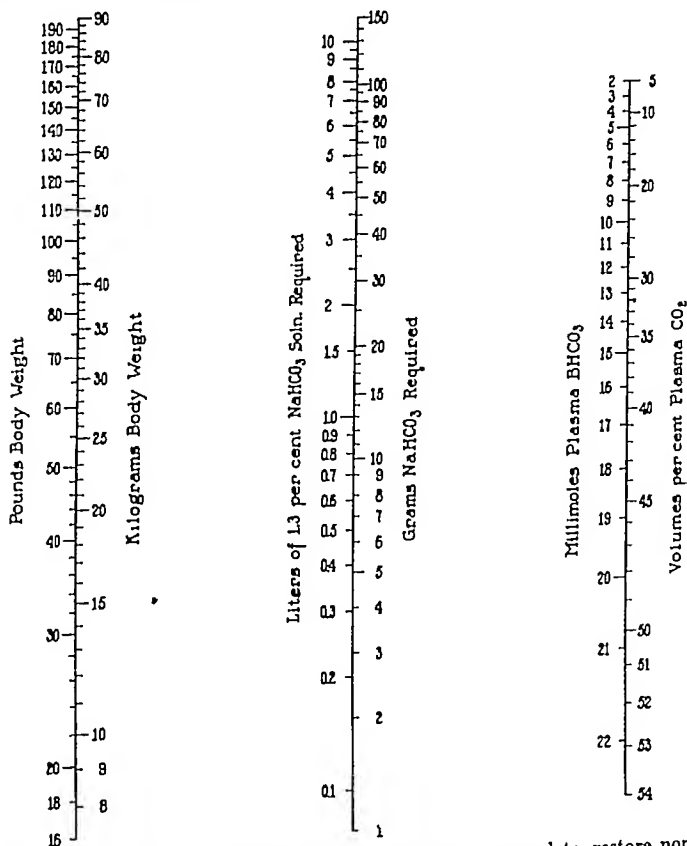


Fig 95—Line chart for calculation of bicarbonate required to restore normal alkali reserve

The only certain benefit of alkali administration is relief from the distress of dyspnea

Although patients with advanced nephritis are unable to conserve salt in the normal manner by cessation of urinary chloride excretion, they have also lost the power to concentrate

chloride in the urine. Consequently, if they receive large quantities of salt without equivalent amounts of water, chloride is retained. For this reason ingestion of salt must be accompanied by enough fluid to insure an adequate urine flow. Large quantities should only be given if there are evidences of salt depletion and dehydration.

**Medicinal.**—The heart often begins to fail early in uremia. Renal excretions may be aided by digitalization. Marked improvement in the condition of the patient is usually noticed after administration of digitalis. It is sometimes necessary because of vomiting to give the drug by rectum or intramuscularly. We have not been convinced that intravenous injection of crystalline strophanthin in glucose has any advantage over ordinary digitalis.

Symptomatic treatment should not be omitted for fear that such drugs as amidopyrine or morphine will further damage the kidneys. Headaches may be combated with amidopyrine (0.3 Gm.) plus codeine (30 mg.) given by mouth. Caffeine in 0.1 Gm. tablets often adds to feeling of well being. It appears inadvisable to administer bromides as they often cause an itching rash which contributes to the patient's discomfort. In case no other drug is able to control headache and restlessness there is no contraindication to the use of morphine.

Vomiting is usually controllable by intravenous administration of hypertonic glucose and an ice-bag placed over the epigastrium. Cocaine in doses of  $\frac{1}{4}$  grain administered by mouth every three hours is often useful. Some patients find sucking cracked ice soothing. Gastric lavage may be tried if other procedures fail, but since it is an uncomfortable treatment for the patient its use is limited. Bismuth subnitrate (1 Gm.) plus sodium bicarbonate (0.6 Gm.) may aid in controlling vomiting. If it becomes uncontrollable all fluids and food must be temporarily withheld and glucose given by rectum. Glucose (5 per cent) with added salt administered slowly by vein (200 cc. per hour) is also indicated. Amytal (soluble) given by vein in doses of 0.2 to 0.3 Gm. may stop vomiting in desperate cases. It is generally unnecessary.

Attempts to aid in removal of toxic substances by means of active purgation have seemed to us a procedure which not only does not accomplish its purpose but is actually harmful. The bowels should move daily and may be aided with some mild laxative, glycerine suppositories or soap suds enemata.

Itching of the skin may be controlled in the manner described under treatment of chronic nephritis.

The mouth should be kept clean with Dobell's solution and the lips well greased with cold cream. A tongue depressor wrapped with gauze should be kept by the bedside to be inserted between the teeth should convulsions occur.

It is often possible by careful therapeutics to allow the patient normal social contacts and duties to within days or weeks of the final uremic coma or cardiac failure. And during the terminal days skilful therapy can minimize the discomfort.

## CLINIC OF DR. WALTER A. BASTEDO

### ST. LUKE'S HOSPITAL

#### FUNCTIONAL DISORDERS OF THE COLON MUCOUS COLITIS

'I SOMETIMES wonder whether it (the colon) is not more sinned against than sinning, for what with attacks from above by purges, attacks from below with douches and frontal attacks by the surgeon, its sorrows are numerous and real." When Arthur F. Hurst penned these lines I had to add that when the professional dietitians and medical columnists adopted the slogan "Treat 'em rough," the poor colon had further to suffer constant bombardment from an excess of figseeds, bran and all that constitutes the great food category known as roughage.

From foods ordinarily eaten the large intestine is subject (1) to distention—by bulk of residue, (2) to mechanical irritation—by indigestible roughage, such as bran, fibers, seeds, husks, etc., and (3) to chemical irritation—by acids and their laxative salts as in fruits by free fatty acids and soaps formed from the oils and fats, by sugars, volatile oils, and other chemical substances. It is further subject to the irritation of the products of bacterial proteolysis and of carbohydrate fermentation, to feces that are hardened, to feces that are fermenting to allergic irritants and to infection. At one end it receives all day long a lot of liquid stuff that smells alright, and at the other end expels once or twice a day a small amount of solid matter that smells to Heaven.

The large intestine is a very sluggish muscular tube with the ileocecal sphincter at one end and the anal sphincter at the

other It possesses the physiologic properties of irritability, contractility and tonicity *Irritability* is sensitiveness to stimuli *Contractility* is power to contract when the stimulus comes In the smooth muscle colon a contraction may be continuous for a long time, as in spasm *Tonicity* or *tone* is the property which makes the muscle resistant to relaxation during the time when it is not actively contracting In a hollow tube like the colon, tone gives the resistance to dilatation and maintains the intra-intestinal pressure when the bowel is not actively contracting High tone in a segment of the bowel makes for narrowed lumen, shortening of the length and reduced capacity, poor tone favors dilatation, elongation and large capacity Except in paralytic conditions, all colons possess irritability, tone and contractility

The colon muscles can contract rhythmically and properly in response to its contents, without help from the outside, that is, if all supplying nerves are severed, but the muscles are also subject to controlling influences from any part of the body through the central nervous system The same may probably be said of its secretory system Thus we can conceive of derangements of function of the large intestine (1) from what is in its lumen, too much or too little in bulk or too much or too little irritating, or (2) from what goes on elsewhere in the body, as a pain in the bladder, an earache, a distressing sight, or a disturbed mind

If the liquid constantly being received at its upper end were passed through the colon without change we would spend our days in the bathroom But a marked function of the colon is to retard and concentrate its contents Therefore, we must get it out of our heads and of our patients' heads that it is normal to have liquid stools, and that cathartic measures are to be rated according to their ability to hasten peristalsis The colon is normally a retarding organ, not a continuously peristaltic one It is not a sewer

As we are talking physiology, we might call attention to the demonstration by Mall that the intestine is the heart or circulatory organ of the liver and of the intestinal lymph

system The mesenteric veins are furnished with valves and every contraction of the intestine forces blood through the portal system and goes to maintain the portal blood pressure and the current through the liver This is important to remember in discussing the use of cathartics

Important, also, is the circulation of the bowel itself The vasomotor nerves of colon and rectum are carried in the autonomic nerves and their stimulation causes blanching of the bowel The dilated bowel tends to have a stagnant circulation, dilated under pressure, as of gas, it may be nearly bloodless The actively contracting bowel has a vigorous circulation, and when there is overactivity, as from a laxative, hyperemia of the mucosa is noted Alvarez states that emotion can cause blanching or blushing of the mucosa The marked changes that take place in the circulation of the bowel, the splanchnic circulation, may have profound effects on the functioning of the bowel and on the distribution of the blood throughout the body

### THE FUNCTIONAL DISORDERS

These are of great interest because a purely functional disorder represents a reaction to a supposed stimulus The reaction comes quickly and goes quickly It resembles a physiologic experiment When an apparently functional disability continues without intermission, we feel that some day the pathologist will detect tissue changes, perhaps in the nervous elements, and thus establish it as organic

The most striking of these with clinical manifestations are hypertonic or spastic constipation, diarrhea, hyperirritable colon, and possibly mucous colitis We exclude those with anatomical abnormalities In the unstable or malfunctioning colon more than one of these conditions may exist together For example, we may have hyperirritable colon with diarrhea with constipation or with mucous colitis, or without any of them, or mucous colitis with hyperirritable colon, diarrhea or constipation, or without them In some of the patients we may find only the usual nervous symptoms that accompany a chronic



disease, in others there may be such profound nervous and emotional phenomena that the relation of cause and effect is difficult to decipher

**Nervous Diarrhea**—In a large percentage of the chronic diarrheas that we see, an etiologic factor is not demonstrable. As a consequence, these are listed as functional disorders. But in many of them, after a time, amebae are discovered, or blood appears, or the mucus is found to harbor pus, or a systemic disease is found to be the cause. It is my belief that most chronic diarrheas have an organic basis. But there is one form that is obviously a true nervous diarrhea. What a nuisance this is to its victim! If my lady goes out to dinner, or is having guests herself her bowels must move. If the student's first class is at 9 o'clock, just at 9 must he defecate, even though to forestall the attack he has already made repeated visits to the toilet. A director suffers at a director's meeting, a professor when he has to lecture. A lawyer is unable to attend court.

The condition is one of looseness of the bowels only under special conditions of self-consciousness or emotional stress. When uncomplicated there are no pathologic elements in the stool, and there is no abdominal distress or diarrhea except in the special circumstances.

These are patients for reassurance, explanation of the real condition, and efforts to ascertain the original emotional cause. They must have treatment for any concomitant bowel trouble, such as habitual constipation or mucous colitis, but in addition require an emergency bowel sedative. For this we employ codeine, to be taken preceding the special circumstances which experience tells will lead to diarrhea. At the outset we prescribe a dose of 0.03 Gm ( $\frac{1}{2}$  grain), but are soon able to reduce this to 0.008 Gm ( $\frac{1}{8}$  grain). In fact, so long as these patients have the remedy with them, they may not need it, but if they are suddenly reminded that the remedy is not at hand or that a toilet is not accessible, the bowels may want to move.

## HYPERIRRITABLE COLON

In this condition there is a tendency to hypersensitiveness and hypertonicity in some part of the colon. The result is either diarrhea as if a laxative had been taken, or spasm which may hold everything back and produce constipation. As a rule only a part of the colon is involved, the hyperirritable area being situated most frequently in the descending sigmoid region or at the rectosigmoid junction. This is the narrowest part of the whole colon and it is especially subject to traumatism. The spasms may also occur in the transverse colon, but are unusual in the ascending. They seem to belong to that part of the colon where the feces are concentrated. Not infrequently the cecum and ascending colon are dilated, not because of atony, but because their normally weaker muscles are unable to force the block produced by spasm.

Kantor, who has found that the same bowel may show at various times or in different parts at the same time, delay, hypermotility, atony, or spasm has suggested the name "unstable colon" for the condition. But I prefer the other term, as it deals with the cause of the clinical manifestations.

**Symptoms**—These may be summed up briefly as abdominal distress, severe recurring abdominal pain, usually constipation but sometimes diarrhea, and pain or cramps from laxative drugs or enemas. The severer symptoms are prone to come in attacks. Of great interest is the fact that accompanying this hyperirritability there is not infrequently an anxiety or fear neurosis, the clearing up of which may abolish the hyperirritability. In some cases there may be mucous colitis.

But hypertonicity, hyperirritability and cramps are not necessarily dependent upon mental stress. They may be the visceral manifestations of an emotive state, but they may also result from roughage or laxative foods, from laxative drugs, from local inflammation or ulceration, and from the irritation of the clinging membranes of mucous colitis. In patients who have habitually bolted their food, we have seen the hyperirritability disappear in a day or two or a week following the

straining of vegetables and the elimination of salads and fruit. This suggests that errors in diet and in eating habits may be the sole cause. Indeed, apprehension might arise in anyone who has frequent repetition of abdominal pain.

People do not die of hyperirritable colon, and the absence of autopsies, together with the rapid yielding to dietary or psychiatric treatment, permits the assumption that it is a functional disorder. Yet, I feel with Alvarez, who remarks, "My impression is that many of them have some lesion in the digestive tract in its nerves or related ganglia." In some the acute symptoms have been found to be allergic reactions.

**Diagnosis**—This rests on severe recurring abdominal distress or colicky pain, the reactions to a barium enema or an ordinary enema, and the x-ray picture. The reactions to a barium enema include increased speed of passage, or temporary stoppage of the flow owing to spasm, the requirement of a decreased amount of fluid to fill the colon, and a crampy pain on distention. An ordinary enema, besides arousing cramps, may not get up very far, or the water may fail to be expelled in the usual way, and may come down in dribbles or in spurts for a long time. The x-ray picture is that of a narrowed colon with irregular walls, more or less obliteration of the haustra or irregular spacing of the sacculations, and localization of spasms.

**Treatment**—The hyperirritable colon must be relaxed and soothed. If the attack is prolonged and acute, the treatment is the same as that for the colic attack in mucous colitis (*q v*). If the attack is prolonged and not very acute, the spasm and pain may be lessened or abolished by a capsule of codeine sulphate 0.03 Gm ( $\frac{1}{2}$  grain) and atropine sulphate 0.0006 Gm ( $\frac{1}{100}$  grain) every few hours, or perhaps by a bromide or a barbiturate. In the more chronic case the treatment of the bowels and the diet is in the main the same as that for mucous colitis. The nervous symptoms require psychiatric treatment just as they would if there were mucous colitis or if there were no colon disorder at all (see treatment under Mucous Colitis).

## MUCOUS COLITIS

This is a chronic condition in which the colon forms ab normal mucus in large quantities. It may be merely incidental to more important lesions of the bowel, such as cancer, tuberculosis or diverticulitis. But there are numerous patients in whom this production of the peculiar mucus is the major bowel manifestation, and it is to these that the clinical term "mucous colitis" is applied. The disease may appear at any period of life from infancy to old age, and is quite commonly found in males as well as females. In the more severe cases, but not by any means in all, it may be accompanied by colicky attacks or various nervous and psychic phenomena, and to these the difficulties of its comprehension may be largely attributed.

**Etiology**—As Sara Jordan has aptly said, "The determination of what is cause and what is effect is an elusive problem in those fields in which a specific chemical or bacteriological cause is not in question." The ascribed causes for mucous colitis are many, and are based on the two theories that it is a true colitis and that it is a functional disorder. On the first theory it is attributed to a specific infection, to the action of normal bowel inhabitants and to the prolonged destructive or irritant action on the mucous membrane of chemical toxic products of food or bacteria. On the ground that it is a functional disorder it has been considered an allergic reaction, a deficiency disease, a purely functional visceral manifestation of a nervous or psychic disturbance, a vagotonic state or a condition of sympathetic or parasympathetic imbalance.

The evidence would suggest that some cases have a true colitis and some have not. That it has a bacteriological cause has not been demonstrated to the satisfaction of the medical profession and none of the other factors mentioned has been proved beyond doubt to be etiologic. Some of the above mentioned causes have been accepted, however, as contributing factors, and their possible influence should be kept in mind. An allergic reaction for example has been demonstrated to

be the cause of the acute colic attacks in a few instances, but convincing evidence is lacking that allergy can account for the persistent formation of mucous casts on the bowel wall. Moreover the acute colics can be explained quite as plausibly in other ways, and in a large number of cases a search for undoubted allergic phenomena has resulted negatively. On the other hand, the possibility of allergy must be kept in mind, for few people go through life without some allergic manifestation.

I believe that in many cases we are not at present able to distinguish between (1) delayed allergic reactions from food products, (2) toxemias from food products, and (3) subinfection from absorbed bacteria, as described by Adams. Any one of these might be held accountable for both acute attacks and chronic toxic states, though probably not for the formation of mucous casts.

**Pathology**—There are no deaths from mucous colitis, and because the premortem clinical interest has been centered on the severe disease that caused the death, the postmortem discovery of the membranes of mucus is incidental and rarely associated with a clinical history of the disease. Likewise, observations on material obtained by the operative removal of a part or all of the colon have seldom been accompanied by mucous colitis histories.

Alvarez observed the mucus in four operatively removed specimens, but does not say why the operations were performed. Cotton, at the Trenton State Hospital, removed many colons and parts of colons for intestinal "toxic psychosis." The lesions found included folliculitis (most common), hyperemia, edema, atrophy of the mucosa and muscular coat, submucous hemorrhages, multiple ulcers most frequent in the cecum, and lymph node enlargement. But he did not relate them to the presence or absence of mucous colitis. Hemmeter found no pathology in two cases, and in two others a catarrhal inflammation, in one of which the lesion extended into the ileum.

The author has found the characteristic membranes in

several autopsy cases. They occurred in all parts of the colon. In one, the cecum and ascending colons were red and granular like a sore throat and these parts were invisible till the mucous film had been removed. In another there was a universally distributed folliculitis, in another a membrane of mucus that looked diphtheritic and extended from the cecum to the splenic flexure. I found it impossible in this case to remove the mucus by forceps or a strong stream of water. Beneath the mucus the colon was hyperemic, granular and eroded. But none of those in whom I found the mucus postmortem was ever a patient of mine for mucous colitis, and in no case had a history been secured of a previous mucous colitis.

Of negative reports, O Rothmann found no lesion in one case, Osler none in two cases in which he readily stripped off the mucus as a continuous membrane, and Hemmeters no lesion in two out of four cases. There are other negative reports.

Of positive reports in clinical mucous colitis cases, Mummery found three types of inflammation, hypertrophic, granular, and chronic catarrhal. Hale White necropsied a case with thin atrophied colon and scattered patches of congestion. In one case M Rothmann found the descending colon, sigmoid and rectum reddened and injected, and the interglandular spaces infiltrated with small round cells. In some areas the mucus not only replaced the epithelial covering but occupied the lumen of the glands, with lateral extensions into the beaker cells. Several cases are reported in which the inflammation extended into the ileum, as in Hemmeters's case. This region has been demonstrated by Herter and others to be at times the site of putrefaction and of streptococcus infection. I have one patient from whom Lane removed the whole colon down to the sigmoid, yet she has passed ropes of mucus up to 18 inches in length, and the sigmoidoscope reveals a decided catarrhal inflammation. In 10 out of 50 cases of "neurogenic mucous colitis" Bockus, Bank and Wilkinson found an inflammatory lesion with the sigmoidoscope. Could they have seen further up the percentage with obvious inflammation

would surely have been larger. Positive reports have also been published by Boas, Einhorn, von Noorden and many others.

Thus we have authentic cases without pathologic lesions and authentic cases with pathologic lesions. This might suggest either that we are dealing with two different diseases, as suggested by Nothnagel, or that the disease in its incipency is purely functional and only by its persistence eventually becomes inflammatory. It is agreed by all that inflammatory changes may result from prolonged derangement of function. Possibly they may result from the treatments administered to overcome functional difficulty, or from constipated feces due to lack of such treatments, or from the irritating effect of clinging membranes of inspissated mucus.

The pathology being uncertain, clinicians are divided into three groups regarding it: those who believe that there is an inflammation, those who believe that it is a functional derangement, and those who believe that there are cases of both types, and that when inflammation is present it may possibly be sequential to malfunction.

Clinically we are frequently unable to determine whether there are lesions or not. Sometimes such are seen through the sigmoidoscope, but often not. I have considered inflammatory those cases showing scablike blood spots or a fair number of leukocytes in the mucus obtained by colonic lavage. On the other hand, it is impossible to determine that there is no inflammation, for the borderline cases do not declare themselves. And since many cases, as we get them, do undoubtedly have colitis, I prefer the old name "mucous colitis" until a better classification is forthcoming.

*The Mucus* — This occurs in thick, tenacious, even leathery, broad sheets, in thin skins or in strings or ropes that may be up to 18 inches in length. The sheets may show the markings of the valvulae conniventes, the strings and ropes, when teased out under water, prove to be tubular casts of the bowel. The odor of the mucus is mucosy, albuminous, musty, foul, putrid, or that of recently dead fish. The color is whitish,

yellow, brown or blackish. The mucus holds degenerated epithelial cells, frequently leukocytes, and occasionally red blood cells. In a number of the author's cases, the presence of noticeable leukocytes has been taken to indicate an inflammatory lesion.

*Bacteria and Vaccines*—For many years we have sought with much trouble for etiologic or contributing bacteria, making vaccines and testing for sensitivity to these by intracutaneous tests. The vaccines to which the patient reacted, and only those we have employed for treatment over long periods. Yet we have never found any flora that seemed specifically connected with the disease, and my years of experience have convinced me that autogenous vaccines are of value only exceptionally and then usually when there is undoubted inflammation of the colon.

It is difficult to explain the peculiar dense mucus. One might postulate a theory that, owing to a secretory neurosis, mucus is secreted in great excess, but that, because of constipation, it fails to mix with the feces, is kept unduly long at the place where it is secreted and like stagnant feces undergoes undue absorption of water. Then this desiccated mucus is subject to compression by a hypertonic bowel against hardened feces, and so membranes are formed. Unfortunately for this theory the membranes form even when the feces are kept soft by mineral oil, and when the bowels are not constipated. Another theory is based on the finding of a slowly acting mucus-coagulating ferment.

*Blood*—Mucous colitis is not a hemorrhagic disease. In a very large number of examinations I have found that free blood in the stool practically always comes from hemorrhoids. At times blood spots will be found in the mucus; they suggest that the mucus has been clinging tightly and has been torn away like a scab. But in all cases where free blood or blood in quantity is coming from above the anus as shown by the proctoscope, a more serious lesion, such as papillitis, diverticulitis, tuberculosis or carcinoma, should be sought for.

*Intestinal Sand*—In colon irrigation returns but almost



never in stools, we have repeatedly found a small amount of hard gritty sand, from whitish to dark brown in color. Mummery found it to consist of about 50 per cent of calcium phosphate with magnesium, iron and organic matter. We have not been able to relate its appearance to any particular type of the disease or to any particular food, except once, when we found the same sand in the crackers that the patient was eating.

*Common x-ray findings* are a movable cecum low in the pelvis, considerable redundancy of the colon and ileal regurgitation.

**Signs and Symptoms**—These patients do not seek help for the colitis. They come for abdominal pain or discomfort, gas distress, chronic constipation or sometimes diarrhea, severe recurrent headaches, failure of physical or intellectual vigor, a falling off in business efficiency, mental depression or nervous breakdown. They have abdominal symptoms and often in addition something the matter with them that causes depression and lack of vigor. They may have noticed strings of mucus in the stools, but commonly do not mention this unless questioned.

*Abdominal Pain and Tenderness*—A little pain or soreness in some part of the colon is usual, or it may be only vague abdominal distress, such as occurs in conditions other than mucous colitis. In any case these patients tend to become "belly conscious." In some there are mild colicky pains and, in a small percentage, paroxysms of the most severe colic in which the patients double up, writhe and almost throw themselves out of bed. Many writers have based deductions as to the nature of the disease on the colic cases only, and have thus added to the confusion regarding it. The colic indicates the hyperirritable colon, and the clinging mucus is presumably the local irritant that provokes the attack, for usually the colic ceases when the mucus is liberated. Soreness without colic may be present for some time thereafter, or may be present following a bowel movement.

Pain of significant intensity is lacking in a fair number of the patients, and even in the hyperirritable may be absent.

for considerable periods, though the abnormal mucus continues to be formed during the painless periods. In the hyper irritable colon type moderate cramps are readily produced by laxatives or enemas.

The more neurotic patients feel pain keenly, and because of persistent localized acute pain and tenderness many have undergone futile gallbladder, appendix and pelvic operations. A contracted and tender segment of the bowel is sometimes palpable, but a tender ropelike sigmoid is not diagnostic, because it is found, or may be developed by deep palpation, in many persons who have neither mucous colitis nor hyper irritable colon.

*Gastric Hyperirritability*—Hyperacidity symptoms and pylorospasm are frequent accompaniments and require consideration in our diets and drug treatment. With many writers, we find achlorhydria not more common than in other groups of the same age.

*Flatulence or Gas Distress*—Not infrequently this is the chief complaint. In many cases it results from aerophagia, for the nitrogen of the swallowed air, being unabsorbable, passes into the colon. Gas may also be due to carbohydrate fermentation, and then it has but little odor. It may also result from protein putrefaction, in which case it is usually foul smelling.

But in normal bowels these foods do not produce undue accumulations of gas; therefore the fault is with the bowel rather than with the diet. So if the restrictions made on account of gas do not soon bring relief, they should not be persisted in. Gas accumulating behind an area of spasm is especially distressing, for the bowel struggles to force it onward, and, as Hurst has shown, it is the distention behind the constriction rather than the spasm that causes pain. Gas in the hepatic flexure may make pain as of a gallbladder, gas in the splenic flexure may make pressure upon the heart. The gas may fill the transverse or whole colon and distend the epigastrium, so that it seems to be in the stomach. Much of

the gas may remain in the flexures in spite of movements of the bowels, but it is usually removable by enema

*Bowel Movements*—Constipation is the rule, yet some have adequate bowel movements and a small number have diarrhea or a bowel readily influenced in either direction. If the constipation is not overcome the patient will not get well, but even in the cases successfully treated for constipation, the mucus continues to form membranes for a long time. On account of the constipation many of these patients become "bowel conscious" and tend to resort unduly to laxatives, enemas, and colon irrigations. They may insist that the bowels pour out liquid stools several times a day, or that an irrigation is a necessity whenever there is abdominal distress.

*Intestinal Toxemia*—Recognizing that the significance of this is a controversial subject and that its importance has been overrated, I would say that I am emphatically of the opinion that the headache, the neurotic manifestations and the condition of mental and physical fatigability are enhanced and at times even produced by the absorption of harmful chemical substances formed in the bowel. It is probable that the bowel with stasis favors bacterial proteolysis and that the damaged mucous membrane permits the passage of deleterious material into the blood. But in addition, because the bowel activity is what drives the portal blood through the liver, there is portal stasis with poor functioning of the liver, which is the great destroyer of poisons absorbed from the alimentary tract.

The toxemia most readily recognizable is that from the products of protein putrefaction, detectable in stools and irrigation returns by an odor suggesting something dead or putrid. Not infrequently this bad odor is discovered by colon irrigation when it is not detectable in the stool. This would suggest that before the upper colon contents reach the lower colon to form stools the chemicals causing the putridity must either have been absorbed or destroyed. There is evidence that they may be absorbed. The only question is: Does sufficient toxic matter to give systemic symptoms pass in an un-

altered condition through the liver, or reach the systemic circulation in oily solution by way of the lymphatics?

In some cases the changes are of the saccharo-butyric type, with acid sour-smelling stools and the development of much gas, but with comparatively little toxemia. The diagnosis of toxemia is highly acceptable to the patient but it should not be indulged in unless its reasonable probability is supported by evidence.

*Fever*—Mucous colitis is not a febrile disease. Occasionally in toxic states there is a rise in temperature of a degree or two, but fever is unusual, and, indeed, because of the depressed vitality the temperature is rather prone to be subnormal. Fever usually means a superimposed acute bowel infection, or an inflammation elsewhere as in tonsils, nasal sinuses or other infective foci.

*Basal Metabolism*—This has varied from low to high and its degree has no direct relation to the disease.

*Genito urinary Symptoms*—In a number of women I have noted that an access of the colitis may be accompanied by bladder irritability. In all of the cases investigated there has been a colon bacillus infection of the urinary tract.

It is a common observation that in women of the emotional type the period of menstruation or the week preceding it is the time for a psychic storm. The menopause is also responsible for nervous phenomena. These facts must be taken into consideration in the treatment of mucous colitis.

*Vasomotor Instability*—These patients feel cold keenly and even when the weather is not cold may have cold hands and feet and chilly sensations. They may perspire easily especially in the hands.

*Echymoses*—These are evidences of capillary fragility. They are seen in women chiefly on the extremities, and may reach several inches in diameter. Such patients also bruise on slight provocation. We have not found any with deviation from normal in the serum calcium.

*Nervous and Psychic Symptoms*—Many of the patients though not by any means all show evidence of some degree

of mental or emotional instability Usually the manifestations are mild and take the form of self-concern and introspection Most patients do not exhibit difficult personality problems But a few develop hysterical outbreaks, a psychoneurosis or nervous breakdown Occasionally one displays such instability of the elative-depressive type as to be on the borderline of insanity Some who may be bright and intelligent socially become self-centered, self-pitying, fault-finding and querulous at home, and wear out both their families and their doctors Many develop phobias, fear of cancer or tuberculosis, fear that their children will be hurt, fear of going into stores, fear of crossing the street, fear that they are "going crazy" Through doubt and uncertainty these develop into anxiety neuroses The neurotic patients exaggerate all symptoms and in their daily affairs make mountains out of molehills Some of them suffer profoundly when in the state of mental depression, and are deserving of pity

An exacerbation of both the mental disturbance and the colitis may be precipitated by an attack of influenza or other infectious disease, by an operation, by a trifling discouragement or defeat, by the assumption of business or social responsibilities, or by worry, as over money matters, a sick or wayward child, a husband who drinks, a skeleton in the closet or a nagging wife Secret worries and clandestine unsocial acts are the worst of all

Nervous persons dislike to acknowledge their weakness, even to themselves, and are prone to attribute their condition to some physical disorder which lights up every time there is a nervous attack "After a time," Peabody concludes, "the symptom and the subjective discomfort that it produces come to occupy the center of the picture and the causative factors sink into a hazy background"

A striking characteristic in these types is fatigability, mental, emotional and physical, the patients being readily brought to a state of exhaustion by serious reading, by visitors, by excitement, by responsibilities, or by physical exertion This

may be a symptom of neurasthenia, but it may be present without other manifestations of neurasthenia

The self indulgent, indolent, weak-willed female is a striking member of the group, yet even the nervous patients are not by any means always of the weaker type. Some of my patients have been women, dominant in social or public life, and strong men, heads of great business enterprises or prominent in a profession. Their condition may be a direct result of a strenuous and fruitful life. After doing big things, their consciousness of inability to cope with the daily responsibilities makes for discouragement, mental depression and fits of dejection. But this type of patient wants to get well, has will power, and will cooperate in every way, and so makes the best patient.

The presence in nervous patients of hyperirritable colon or mucous colitis does not establish a cause or effect relation in either direction, yet many have assumed that mucous colitis is of neurogenic or psychogenic origin. I do not think this usual and should like to quote authorities on the subject.

In a study of the "neurogenic type of mucous colitis," Bockus, Bank and Wilkinson found nervousness of some type present in practically every case, the patients being often of hypersensitive, impressionistic nature, but they were able to classify only 48 per cent of the patients as neurotic, psychoneurotic or neurasthenic. Sara Jordan found 62 per cent with a positive neurogenic history, and 38 per cent without such history. Jacobson says, "That the nervous system has much to do with the initiation of mucous colitis and spastic colon is just a loose general impression." Boldyreff and Stewart find that "Physiologists have failed to prove that the secretion of mucus in the intestine can be traced to psychic causes." (We might here interject Alvarez's suggestion that it is one thing to do a psychological experiment by frightening a young woman in the laboratory and quite another to read in the papers that her friend had eloped with another woman.)

Von Noorden says "Neither constipation alone nor neurasthenia alone nor the common combination of these states can produce colica mucosa (mucous colitis). Frequently a

cure of the digestive disturbances and an improvement in the general nutrition lead to an amelioration or a complete cure of the nervous symptoms without any other treatment" Mummery says, "There are a number in which the other symptoms are well marked, but the patients are not in the least nervous" Alvarez calls attention to the fact that "the disease sometimes appears in middle-aged men who are not at all nervous" It also occurs in children, and Sara Jordan finds that "the younger patients show a markedly diminished tendency to associated neurogenic symptoms" Furthermore, a vast number of persons have nervousness and emotional instability with constipation but without either hyperirritable colon or mucous colitis

Among the older psychiatrists who have opposed the theory of neuropsychogenic origin for mucous colitis, we might mention Alt, Fleming, Griesinger, Krafft-Ebing, Schule and van der Kolk Pierre Janet says, "In severe forms of psychosis, gastro-intestinal manifestations like those of mucous colitis are rare The confirmed neuropath is always better nervously when undergoing strain, exertion, pregnancy, operation or acute illness The opposite is true of patients with mucous colitis They are made worse by any stress or strain"

On the other hand we recognize that the digestive tract is highly responsive to changes in the emotional state This can easily be proved in the laboratory and it occurs in the experience of most of us It is readily understandable, for example, that under nervous stress the defecation reflexes may fail to make a proper correlation between the various mechanisms involved in producing a stool, and that as a consequence constipation is set up Often repeated this may in time become a chronic state, even with inflammation In this connection Adolf Meyer says, "With self-suggestion or suggestion by others it is possible to produce structural alterations"

In any event, whether these patients are classed as psychopaths or colitis cases, or what you will, the failure to treat the bowel means that they will not get well Or as Henry expresses it, "Little progress can be made in the readjustment

of the total individual until the physiological processes are altered." Psychiatric methods seem to give temporary benefit, but I have yet to see any case of mucous colitis permanently cured by psychiatry alone. Surely we must class mucous colitis as something other than a mere symptom of a nervous or mental state.

**Our Theory**—What is the relation of the bowel trouble to the nervous system? Neurologists consider that neurasthenia or a psychoneurosis requires two conditions for its production, namely, an underlying neurotic personality and a provocative factor, one of the most pronounced of which is fatigue. Yet perhaps the neurotic personality is not an absolute requirement, for Fere states that "fatigue often provokes ideas of negation, persecution and disparagement," and, according to Dubois, "exaggerated fatigue may induce neurasthenic states in the best balanced individual." Therefore, without accepting the theory that a neurotic personality or emotional imbalance is a necessary part of mucous colitis, though often present, but agreeing that a great provocative factor for nervous and psychic reactions is fatigue, it is my opinion that *mucous colitis acts as such a provocative factor because it is an important producer of fatigue*, either of itself or through the production of toxic substances.

**Diagnosis**—Neither constipation, nor intestinal putrefaction, nor abdominal pain nor a psychoneurosis tells of itself that mucous colitis is present, and there is no diagnostic criterion for mucous colitis other than the characteristic mucus. The presence of mucus as such is not sufficient for diagnosis. It must be mucus that forms a membrane on the wall of the colon and is passed as strings and sheets. It is evidently not the freshly secreted mucus from a cathartic enema or irrigation, or from acute inflammation. Likewise shreds of mucus clinging to a constipated stool do not establish the diagnosis.

The mucus may be recognized in a submitted stool or brought in by the patient, perhaps in the belief that it is a worm but not infrequently it is discovered only by a colon



irrigation It is our belief that those who do not employ colon irrigations for diagnostic purposes must fail to recognize many of the cases

Various roentgenologic and sigmoidoscopic pictures have been described as diagnostic In our opinion there is no diagnostic roentgen finding, and in most cases no sigmoidoscopic However, sometimes the sigmoidoscope reveals in the upper rectum or sigmoid region a marked dryness or a catarrhal inflammation and, in addition, the clinging tenacious mucus

In a chronic disease of this kind the presence of organic disease of the large bowel or of other organs should be repeatedly looked for, especially should one try to exclude lead colic, amebiasis, cancer, tuberculosis, diverticulitis, papillitis, appendicitis, cholecystitis and pelvic disease On the other hand, care must be exercised lest acute or chronic abdominal pain caused by mucous colitis be interpreted as appendicitis, cholecystitis or other surgical condition

Moreover, it must be kept in mind that maladjustment to the environment and deranged colon function may in reality indicate systemic disease in a more or less latent state, *e g*, tuberculosis, thyroid or pituitary disorder or the sequelae of encephalitis

Severe colic attacks are unusual, therefore if mucous colitis is sought for only when there is colic, many cases will be missed, if it is looked for in every patient with vague abdominal pains, nervousness, depressive emotional states, persistent lassitude or a falling off in efficiency, it will often be discovered

**Treatment**—Mucous colitis is chronic, is a cause of ill health, inefficiency and unhappiness and has no specific treatment, therefore its therapy strikingly illustrates the principle of treating the whole patient rather than just a disease Every factor that may contribute to poor nutrition, lowered vitality or fatigue must be eliminated The teeth and mouth must be put in order, a flabby abdomen supported by a belt, an irritable bladder or dysmenorrhea cared for Any surgical condition, such as purulent tonsils, infected nasal sinuses, a diseased gall-

bladder or appendix, a retroverted uterus, a torn and lax peritoneum, an anal fissure or painful hemorrhoids, should be attended to, for such may render medical treatment ineffective. But as mucous colitis patients do not bear operations well, surgery should be preceded by efforts to get them into as good a condition as possible.

There is no specific treatment, therefore the therapy is directed by the condition of the patient at the time. As the disease is very chronic, it will tax all the therapeutic powers of the physician as the months go on. Rash is he who would criticize another's prescriptions under such circumstances. Two facts stand out prominently: (1) That retained mucus is harmful mucus, and (2) that the cure requires a long time. I am wont to tell my patients that a cure cannot be obtained under a year.

The therapy consists of: (1) Treatment of the attacks of colic. (2) Treatment between the attacks of colic, or when there is no colic.

**Treatment of the Attacks of Colic**—This resolves itself into measures: (1) to promote evacuation of the mucus, and (2) to relieve pain and neurotic reactions.

*To promote evacuation of the mucus* one may employ a large dose of castor oil by mouth, or calomel and salts, and enemas or gently administered colon irrigations of physiologic salt solution.

*To Relieve Pain and Neurotic Reactions*—For the spasm one may use heat to the abdomen, hot enemas or colon irrigations (110–115° F), hot drinks, atropine or the nitrites, to lessen the nervous reactions, codeine, a barbiturate or bromides, all in large doses. Favorite with the author are: Codeine phosphate or sulphate 0.3 Gm ( $\frac{1}{2}$  grain) with atropine sulphate 0.0006 Gm ( $\frac{1}{100}$  grain) in a capsule to be taken every hour for three doses or till relief is obtained, sodium nitrite 0.13 Gm (2 grains) every hour, and 2 to 3 Gm (30 to 45 grains) of a bromide. The codeine and atropine or soluble phenobarbital may be given by hypodermic. Nitroglycerin acts promptly when placed under the tongue.

Often the combination of castor oil by mouth, codeine and atropine hypodermatically, an electric heat pad to the abdomen, and a hot colonic lavage will be followed by relief and sleep. If there is temporary relief followed by recurrence, another colon irrigation may be given, after which a pint of warm olive oil is injected into the colon to be retained, and the drug treatment is repeated. This is often followed, a few hours later, by the passage of the oil and abundance of mucus, with disappearance of the colic and no recurrence for a long time.

**Treatment Between Attacks of Colic or When There is No Colic**—This resolves itself into diet, the treatment of chronic constipation, methods of dislodging the mucus, the treatment of the neurotic or psychoneurotic state, and attention to anemia and other systemic conditions. When present, the recognition and treatment of allergy are important.

*Diet*—In the long run a good mixed diet is the best, but at the outset it may be wise to adopt a bland diet, one that excludes gastro-intestinal irritants like whole wheat bread and other branny foods, salads, coarse vegetables, and fruits but not fruit juices. All vegetables except the starchy ones should be strained. Such a diet is constipating and must be supplemented by measures to move the bowels. But the coarse, indigestible foods that constitute roughage will do more harm to these injured colons than any mildly laxative drug. After a time the list of vegetables may be increased and cooked fruit without seeds allowed. Then we stop straining the vegetables and add a salad of lettuce or endive with tomato, and raw orange, grapefruit, apple, pear, peach and melon. The skins of fruits should be removed. If there is putrefactive toxemia, the diet should exclude meat and eggs, if flatulence, it might exclude fruits and starchy vegetables, and even bread, for a time. If milk is well borne, it should be taken freely. A patient who carefully masticates vegetables and fruits can graduate to these foods more quickly than one who is careless.

In all cases the diet should be ample, for these patients are prone to undereat because of fear that this, that or the

other food will do harm. Neither the bowels nor the patient will get well on inadequate food. Moreover, the diet must satisfy the palate so that the patient will eat it and must therefore give some latitude for choice. Monotonous specified meals are seldom adhered to for more than a brief period. It is a good plan to have patients from time to time bring in a list of the foods and fluids taken in a three-day period, for such a list frequently reveals unconscious dietary errors.

*Avitaminosis*—The possibility of this from failure to absorb the vitamins, or because of their absence from the food, makes one press the use of cod liver oil or its substitutes, yeast preparations, tomato and other fruit juices, butter and milk. It is of more than passing interest that mineral oil, being unabsorbable, carries out some of the fat soluble vitamins, A, D and E. Indeed, as the result of her experiments, Rowntree recommends that mineral oil should never be given unless accompanied by generous quantities of vitamin A, as in butter.

*Constipation*—Space does not permit consideration of the whole treatment of constipation, but diet comes first in importance. In addition I would say a word about the use of drugs. Doubtless in protest against the oldtime prescribing of strong cathartics, the New Dealers in medicine have branded the prescribing of cathartics as a medical crime. But what if their other measures are unsatisfactory? I have found this to be the case in numerous instances. Alvarez notes that "Even the bulky diets tend, after a time, to lose their efficacy." When the bowels do not move in response to the permissible diet the profession has done worse things than prescribe laxatives. It is true patients with chronic constipation readily acquire the cathartic or enema habit, for they seek relief from an abnormal and distressing condition but education as to what is proper functioning of the bowels and as to how this may be secured may bring about the correct use of both laxative drugs and laxative foods. Hurst, Alvarez, Lawrence and McCance and many other writers have pointed out that roughage diets do

more harm to a sick or sensitive colon than any mild chemical laxative

For the relief of the constipation bland agents of the softening and bulk-producing group may be tried, such as mineral oil and agar. But usually agar does not suffice, and when this is so I like the addition of a tonic laxative in the form of cascara-agar or cascara-bassorin. Milk of magnesia in small doses at night carries down water and is a useful softener and bulk producer for some patients. Morning salines help for a time but give entirely abnormal stools. Phenolphthalein may also be helpful, but it is irregular in its action and is prone to make unhealthy loose stools, especially is this true of the mixtures of phenolphthalein, magnesia and mineral oil. But constipation is not cured by changing it to diarrhea. Best of all are the tonic laxatives, cascara, senna, rhubarb and aloin. They act essentially on the colon and not on the small intestine. They do not produce inflammation and they continue effective for years in low dosage. Their dose is properly kept low or they will produce the condition of hyperirritable colon. Drastics, that is, drugs that readily produce inflammation, such as podophyllin, colocynth and jalap are not employed.

An occasional dose of castor oil, or calomel followed by salts, greatly benefits these patients, not only by loosening and carrying out the mucous sheets, but possibly also by removing toxic material and by improving the portal flow through the liver. These drugs begin their action high up in the small intestine and so make a profound change in the circulation of the whole bowel and the liver. A weekly enema of saline, but not soapsuds, may also be advantageous.

Painful hemorrhoids, an anal fissure or severe anal cryptitis may make difficulties. They can be treated by the nightly instillation into the rectum by means of a soft rubber ear syringe, of 60 cc (2 ounces) of olive oil to be retained over night, by the application of a 5 per cent ointment of ethyl aminobenzoate in petrolatum album, or by the insertion of a suppository of 0.3 Gm (5 grains) of ethyl aminobenzoate. The feces should be kept soft by mouth doses of mineral oil.

Should this treatment not suffice a proctologist is a necessary help

*To dislodge the mucus* that adheres so tightly to the bowel wall and to clean out the cesspool materials, we give colon irrigations and an occasional dose of castor oil, mild mercurous chloride followed by salts, or salts alone

We give colon irrigations two or three times a week at first, and later once a week or once in two weeks. An elaborate apparatus is not required. Our method is to use several gallons of plain warm water by the two-tube process, using as the inlet tube a catheter, number 20 French, and as the outlet tube a velvet eye, closed-end rectal tube, number 30 French. The inlet tube is inserted about 6 inches, the outlet tube 4 inches. The bag is hung low to give not more than 2 feet of pressure and the water is run in very slowly, usually about an hour being allowed for an irrigation, as the clinging mucus may take a lot of soaking before it is dislodged. For the first gallon the patient is placed on the left side and for the rest of the irrigation on the back. It is desirable for the bowels to move before the irrigation, and if they have not done so already they are cleansed with a plain water enema, and then a short time is allowed for the defecation reflexes to quiet down before the irrigation is given. We never give irrigations to move the bowels, but for the purpose of cleansing the region above the defecation area and irrigating the bowel wall as far up as the water will reach, and just as a stomach is lavaged with water until it is clean, so do we try to lavage the colon until it is clean (See author's article on Colon Irrigations in the *A M A Handbook of Physical Therapy* )

Colon irrigations are not necessary in the treatment any more than throat irrigations are necessary in tonsillitis, strapping in pleurisy, or heat in lumbago. But they are a great help.

*Nervous or Psychic Manifestations*—In this group the psychiatric treatment is the same as that for similar patients who do not have mucous colitis. The emotionally unstable patient, the physician must handle with the utmost kindness

and consideration, but also with decision. Such patients become worse when found fault with or treated brusquely. As they take everything quite seriously and readily misconstrue what one says, the wise physician avoids making dogmatic statements or pointed remarks about foods, remedial measures or the methods of other physicians.

We must keep in memory Kantor's three R's, Reassurance, Reeducation and Relaxation. We strive to expel from the minds of these patients the fear of organic disease, to fill them with hope, to correct their distorted views of their condition and of how a bowel should act and to point the way for them to overcome their habitual tenseness. Success sometimes depends on one's ability to induce them to talk about their secret worries, to pour out their pent-up emotions, and on one's power to stimulate them to meet life's troubles in a grown-up way. There is no reason why we cannot all be psychiatrists with most of our own patients, for, as someone has said "Few people are so deep that they require special technic to get at the bottom of their minds." But it does take patience and a sympathetic attitude.

To say to one of these unfortunates, "There is nothing the matter with you below the neck," or "If you would stop thinking of yourself you would be alright," is not playing ball, and it renders the outlook hopeless. To classify the patient as a "neurotic fool" or a "neurasthenic" ends the physician's usefulness, for then he ceases all further investigation and lowers or abolishes his subsequent interest in the patient.

We instruct the patient never to overdo, never to carry anything, physical, emotional or mental, to the point of over-fatigue. We try to arrange occupation, recreation and rest in proper proportions without allowing the patients to coddle themselves, and we do not permit extra responsibilities, such as political, club or church committee work, outside educational courses, or teaching Sunday school. We insist on early retirement and a complete period of rest and relaxation each day, usually after the midday meal, or before dinner. Dur-

ing the rest period a hot-water bag, an electric pad or a hot compress may be applied to the abdomen. The object is to obtain as complete mental and muscular relaxation as possible. After the bowels, diet and daily habits are under good regulation, we may advise a change of surroundings to get the patient away from oversolicitous or nagging friends or from the wear and tear of home or business.

If, at the outset, patients are too sick to carry out this plan, it is seldom possible to get them well in home surroundings, and in such event they are placed for a time in the hospital where they will be under personal supervision, where one can talk with them, encourage them and watch them, and teach them how to relax, and where one can keep the family away as much as seems wise. Here they are given cold spinal douches, cold rubbings up and down the spine, cold packs, massage, hot applications to the abdomen during a part of the day, or other forms of physical therapeutics, as well as care of the diet and bowels and plenty of rest. If one's local hospital is not satisfactory for this class of patient, one can send the patient to some well conducted sanatorium where fads do not prevail. When the patient returns the home treatment will have to be resumed for all that spa or institutional treatment can do is to give the patient a fresh start. The effects may be removed, but often not the cause.

For the nervousness we may give about 13 Gm (20 grains) of a bromide after the morning and evening meals, or when the irritability and sensitiveness are most noticed by the patient. I dislike the continued use of phenobarbital for these patients as it depresses both their vitality and their spirits and they soon become habitues. For the insomnia which must be overcome by drugs for a period we give bromide, carbromal or barbital. Valerian is helpful and a good nerve cocktail to tide them over special stresses is a teaspoonful or two of a mixture of equal parts of aromatic spirit of ammonia compound tincture of lavender and spirit of chloroform. This is also a good carminative. Strychnine is usually contra-



indicated as the patients are already in a state of overtone, but this should be determined by testing their deep reflexes

**Conclusion** —I believe that in a large number of mucous colitis patients a practical cure is possible, but for cure it is necessary to continue the bowel treatment for a long time I have seen many of them in serious nervous states who, after the cure of the bowel trouble, ceased to be more than normally nervous To treat these patients as disagreeable neurasthenics and to neglect the bowel is a great mistake

The chronic invalids of this class, whether highly neurotic or not, come to us because they are ill, otherwise they would not seek a doctor If the family is out of sympathy, the doctor must not be Many of them are misfits, or victims of circumstances or of an overweening and misdirected ambition They need not only the care of their bowels and their general health, but in addition such psychiatric treatment as they would be entitled to if they did not have mucous colitis They consume a lot of time and cannot be hurried But is it not one of the most pleasurable functions of a physician to change discouragement to hope, unhappiness to happiness, inefficiency to efficiency, and invalidism to comparative health? For many of these patients the family physician can do much Indeed, a knowledge of the family affairs and sympathetic discussion of them will often prove more helpful than any treatment that can be devised as the result of laboratory tests

## CLINIC OF DR. WENDELL J. STAINSBY

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### THE PRACTICAL VALUE OF THE ERYTHROCYTIC SEDIMENTATION TEST

WHEN freshly drawn blood is treated with an anticoagulant and allowed to stand, the erythrocytes tend to separate from the fluid elements and to settle toward the bottom of the container. When specimens from healthy individuals are used, the rate of fall is slow except when physiologic conditions as pregnancy and menstruation are present. On the other hand, when samples of blood are taken from patients suffering from infectious diseases, anemia, or certain noninfectious conditions, the rate of fall of the erythrocytes is increased beyond that found in normal individuals. Of considerable importance to the clinician is the observation that the increased rate of fall is proportional to the activity of the disease process rather than to the size or extent of the lesions.

A comparison of the patient's temperature and sedimentation rate indicates that there is little if any direct relationship between them. It is true that when the temperature is high, the sedimentation rate also tends to be high, but there is great variation in different types of diseases. In infectious diseases which run a limited course such as typhoid or pneumonia, the temperature and sedimentation curves run a somewhat parallel course with the exception that the temperature tends to return to normal sooner than the sedimentation rate. In more chronic conditions such as some manifestations of rheumatic fever or tuberculosis, the temperature may remain

normal for several months while the sedimentation rate remains elevated. In rheumatoid arthritis, the patient may never have fever throughout the entire course of his disease and yet have a markedly increased sedimentation rate. Similar results are obtained when sedimentation rates and Schilling differential white blood cell counts are compared.

The sedimentation test is not specific for any one disease or group of diseases. Infectious diseases, however, have the most consistent and highest sedimentation rates, and it is with this group of pathologic conditions that an estimate of this rate offers the most information to the physician.

#### TECHNIC FOR SEDIMENTATION TEST

Many methods for performing the sedimentation test are in common usage, only a few of which are satisfactory. In the first place, an anticoagulant should be used that does not in itself affect the sedimentation rate. Heparin meets this requirement while sodium citrate does not. In the second place, a correction for anemia should be made. It has been previously stated that anemia affects the sedimentation rate, and as anemia is frequently a progressive phenomenon during the course of an infectious disease, results would be misleading unless corrections were made for it. Rourke and Ernstone have devised a technic which has proved to be highly satisfactory, and readers are advised to consult their original article<sup>1</sup>.

#### APPLICATION IN SPECIAL PROBLEMS

**Question of Neuroses**—In private practice as well as in the institutional care of patients, the question occasionally arises as to whether a patient's complaints are on a functional basis or due to some organic disease. The test has a limited value in solving this problem. A definitely elevated sedimentation index (0.5 or higher) indicates organic disease providing the usual causes of error such as pregnancy and minor upper respiratory infections are eliminated. When such elevated sedimentation indices occur, considerable effort should be made to determine the underlying morbid process. A normal

sedimentation rate on the other hand does not rule out organic disease, as the condition may be due to some pathologic process that does not affect the rate

**Rheumatoid Arthritis**—The test is particularly useful in following the course of the disease in patients with rheumatoid arthritis. The writer in collaboration with E. E. Nicholls has reported in detail their experiences with the sedimentation test in this disease, and has found it a valuable diagnostic and prognostic aid. In this condition, the temperature is seldom elevated, while the total or Schilling differential white cell count is frequently within normal limits. The patient's symptoms are an unreliable index of the activity or progress of the disease, as they are very easily modified by weather conditions, rest, and exercise. Likewise, examination of the joints without additional aid sometimes misleads even the expert student of arthritis, as some of our active and most rapidly progressing cases have little swelling and tenderness of the joints. The sedimentation test is, therefore, the most reliable aid that the physician has in determining the three important questions that concern the welfare of his patient. In the first place, Is the disease active? Secondly, How active is it? Thirdly, Is the patient improving or getting worse under the treatment that is being administered to him? A sedimentation index 0.4 or less indicates that the disease is inactive or nearly so, an index of 2.0 points to an active disease while decreasing indices at intervals show the favorable response of the patient to treatment. With more general employment of the sedimentation test in rheumatoid arthritis, it is probable that many questionable forms of therapy will be discarded and more rational ones adopted.

**Rheumatic Fever**—In rheumatic fever the sedimentation index employed in conjunction with temperature records and Schilling differential white cell counts provides additional aid to the clinician in determining the activity and course of this important disease. A case of rheumatic fever should not be considered inactive until these three indices have returned to normal. Experience has taught physicians the importance

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of determining the presence or absence of rheumatic infection particularly in children as too early resumption of exercise following an attack undoubtedly increases the patient's chances of a relapse and possibly promotes cardiac damage

**Pulmonary Tuberculosis**—In pulmonary tuberculosis, the sedimentation test is a distinct aid to those familiar with its use. In this disease, however, secondary infection of the bronchi by organisms other than tubercle bacilli takes place, especially in advanced cases. The question then arises as to how much of an elevated sedimentation rate is due to tubercle bacilli and how much is caused by the secondary invaders. As long as this factor is always kept in mind, however, the test may be utilized with considerable diagnostic and prognostic aid to the clinician.

In detecting early tuberculous infection, the sedimentation test is sometimes of value. In general medical clinics where this test is frequently employed, an abnormally high sedimentation rate has prompted the physician to thorough and extensive search for an infective process, leading in some cases to a detection of an early lesion of tuberculosis.

The sedimentation test is also of help in following the course of the disease in any particular patient, and is of considerable value when patients are being treated at regular intervals by pneumothorax. When used in conjunction with sputum examinations and temperature records, a satisfactory picture of the course of the disease is obtained. In the ambulatory treatment of tuberculosis by pneumothorax, the sedimentation index is more reliable than the temperature for the obvious reason that the temperature varies considerably during the course of a day, while the sedimentation index remains constant.

A normal sedimentation test at the time when a patient with tuberculosis is considered to have reached an arrested or inactive stage of the disease affords assurance to the physician that his impression is correct. A high index, on the other hand, does not indicate activity of the disease, for secondary infection in the bronchi may be responsible.

**Acute Febrile Diseases**—In acute infectious diseases that run self-limited courses, such as typhoid and pneumonia, the sedimentation test offers little if any help beyond that supplied by temperature records and Schilling white blood cell determinations, and its routine use in these diseases is not recommended

#### SUMMARY

The sedimentation test is a valuable diagnostic and prognostic aid to the physician, especially as regards chronic infectious diseases. At times, it is a help in differentiating between functional conditions and organic disease. In rheumatoid arthritis, it is the most reliable test for estimating the activity of the infectious process and in determining the response of the patient to therapeutic measures. When employed in conjunction with temperature records and Schilling differential white blood cell counts, the presence of active rheumatic fever may be definitely determined. In pulmonary tuberculosis, it is of value in detecting the presence of the infection, in following the course of the disease, and in establishing the fact that the process is no longer active.

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## CLINIC OF DR. HAROLD J. STEWART

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### THE OCCURRENCE OF HEMOPTYSIS AS A SYMPTOM OF ACUTE HEART FAILURE IN THE PRESENCE OF MITRAL STENOSIS

I wish to discuss one symptom which occurs frequently in the life history of patients suffering from mitral stenosis and one which is frequently misinterpreted. I refer to the symptom of blood in the sputum, and the more profuse expression of it, of hemoptysis. There are five situations all different, in which blood appears in the sputum of patients suffering from mitral stenosis which might give rise to difficulty of interpretation of this symptom, and the prognostic implications in each instance are different. I refer to its occurrence (1) in the course of a primary pneumonia (2) to its occurrence as a sign of pulmonary infarction, (3) to its occurrence in pulmonary edema, (4) to its occurrence in the type of paroxysmal pulmonary hemorrhages described by Oppenheimer and Schwartz,<sup>1</sup> and (5) finally that which concerns us at this time, to its occurrence as a sign of acute cardiac failure. Hemorrhages in mitral stenosis due to pulmonary tuberculosis, bronchiectasis, varicose veins, and carcinomatosis will not be considered here. It is its occurrence in the last instance enumerated above, namely, as a sign of acute heart failure, that the sign is frequently misinterpreted as being due to pulmonary infarction and for this reason warrants analysis.

The case of the first patient I shall present contrasts in one patient the occurrence of this symptom, hemoptysis, in three of the situations mentioned above, namely, as a sign in

pneumonia, as a sign of pulmonary edema and finally as a sign of acute heart failure I shall give only the data necessary to create for you the clinical picture which he presented

The patient, R N, a white male, thirty-eight years of age, was first admitted to hospital November 11, 1933, and discharged November 30, 1933. He complained of cough and expectoration of two weeks' duration, intermittent rise of temperature for two weeks, edema of the ankles for three days, and acute dyspnea and orthopnea for five hours

**Family History**—The family history was of no significance in its bearing on the patient's illness

**Past History**—The patient had never suffered an attack of rheumatic fever, chorea, or acute tonsillitis, he did not admit to having exhibited the symptoms of other manifestations of rheumatic infection

**Cardiac History**—When the patient was admitted to the United States Army in June, 1917, cardiac disease was not detected. He did not go over sea. The examination when he was discharged from the army in March, 1919, revealed a "cardiac lesion." He was *without* symptoms at that time and disregarded the advice to avoid overexertion. In the next few years he became aware of slight palpitation and fatigue on overexertion. In February, 1924, a first break in compensation, characterized by palpitation, occurred, for which he was admitted to the Brooklyn Naval Hospital for two weeks. On discharge, he limited his activities and took digitalis intermittently. A second break characterized by *palpitation* and *dyspnea* occurred in October, 1929, for which he was admitted to the same hospital for three weeks, after going home he remained in bed until February, 1930. On beginning to get up a third and similar break in compensation occurred for which he was treated at home by rest in bed and the use of digitalis. When he recovered from this attack he took digitalis at irregular intervals again and remained well, without working however, until the onset of a pulmonary infection on October 30, 1933, with extreme fatigue and chilliness. Later during this day the patient experienced a shaking chill and rise in temperature to 101° F occurred. Cough with sputum was present, as well as palpitation of the heart. The next day he felt better but when he got up in the evening his temperature rose to 103° F. Digitalis and rest in bed were prescribed. The temperature gradually fell to normal and on November 5th, he began sitting up and discontinued taking digitalis. On November 5th, 6th, and 7th, the afternoon temperature rose again to 101° or 102° F, on November 7th, edema of the ankles was observed. On November 11th, the temperature was again normal and the patient got up, in the evening, however, when the temperature rose to 102° F and dyspnea and orthopnea appeared the patient was admitted to New York Hospital. Since October 30th, cough had been productive of sputum which was at times "rusty" and at other times blood-streaked. Digitalis had not been taken since November 5th, with the exception of 15 drops of a tincture on November 10th.



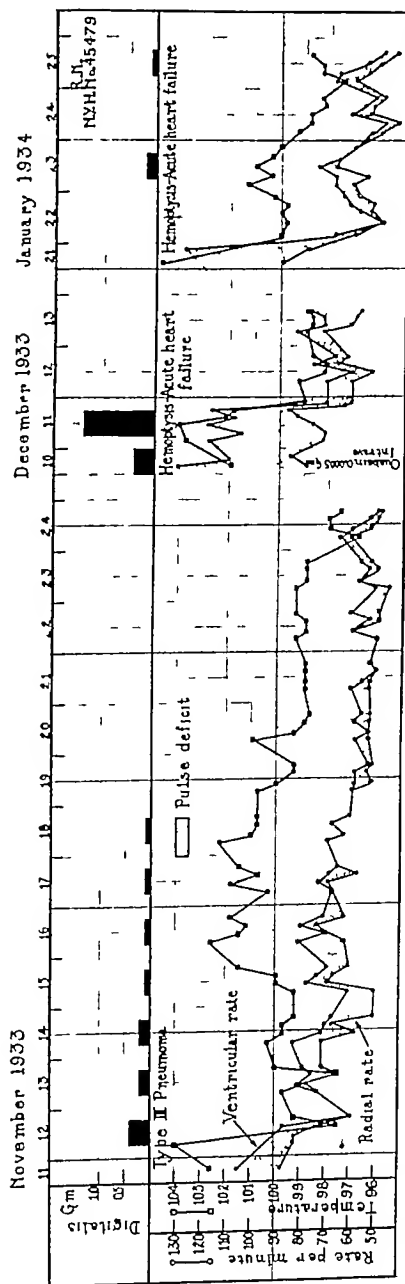


Fig 96—In this figure are shown data relating to three admissions to hospital of patient R N, New York Hospital History No 45479. Rectal temperatures are indicated by open squares and mouth temperatures by closed squares. It shows the rise in temperature and increase in ventricular rate associated with two attacks of acute heart failure, the presenting symptom of which was hemoptysis (December 10, 1933, January 21, 1934).

cent myelocytes. The ventricular rate had been maintained at a slow rate by the continuance of digitals and on November 24th the liver was felt only at the costal margin. Convalescence was without incident and the patient was discharged November 30 1933. The urine on discharge was free of albumin and the sediment did not contain formed elements.

In summary, the outstanding events in this episode were the sudden onset with chill, rise in temperature, expectoration of rusty sputum and sputum containing blood, signs of consolidation of the lower lobe of the right lung, followed by signs of involvement of the left lung, marked leukocytosis, and the isolation of Type III Pneumococcus from the sputum. Associated with this was cardiac insufficiency.

In the next two episodes hemoptysis was of different etiologic origin from that just described. On the *second admission* December 10 1933 the complaint was of spitting blood and of having suffered a chill. The patient was discharged from the hospital as has been stated on November 30th and was up around the house but did not go out. Three days later he began to cough. Two days later still he began to raise sputum streaked with *bright red blood* and five days later still he was raising about 4 *tablespoons of "pure" blood* a day. Two days later while walking to the bedroom from breakfast he suffered a shaking chill associated with dyspnea orthopnea and cyanosis. He wished the windows to be opened in order to breathe sufficient air. During the day he expectorated  $\frac{1}{2}$  *pint of "pure" blood* this symptom was not associated with pain in the chest at any time. He was admitted to the hospital December 10 1933.

On examination he appeared acutely ill. The temperature was 102° F (rectal) the ventricular rate was 132 per minute and the pulse rate 84. The respiratory rate was 28 per minute. Marked dyspnea orthopnea and cyanosis were present. Perspiration was profuse. The vein of the neck were greatly distended. The heart was enlarged both to the right and to the left on percussion and rapid auricular fibrillation with a wide pulse deficit was present. The systolic blood pressure was 86 mm of mercury and the diastolic 60. Signs of mitral stenosis and insufficiency were present. Examination of the lungs revealed no abnormality on percussion. Many inconstant musical râles were heard over the whole chest both anteriorly and posteriorly and a moderate number of moist râles at both bases, posteriorly. Examination of the abdomen revealed no sign of ascites the liver was palpable 6 cm below the costal margin. Edema of the extremities was not present. Chinabain 0.0005 Gm., was given intravenously followed by the use of digitalis by mouth although 400 cc of blood was removed by vein venous distention persisted. The count of the white blood cell was 20,000. Of these cells 51 per cent were adult polymorphonuclear in form 33 per cent immature polymorphonuclear cells 10 per cent lymphocytes 5 per cent monocytes, and 1 per cent eosinophil. The count of the red blood cells was 4,000,000 hemoglobin 85 per cent

(Sahl) The urine contained a trace of albumin, and hyaline and granular casts were present in the sediment. After digitalization (Fig 96, December 10th and following), the patient was improved the next day and by evening the temperature had fallen to normal and did not rise again, and the ventricular rate fell to 70 and did not rise above the normal level again. There was no cough and *no sputum* after admission to the hospital. At no time did the patient experience pain in the chest. x-Ray examination of the chest showed marked general mottling (Fig 97, A). On December 14, 1933, the count of the white blood cells was 8600 only and did not increase again. On December 18th, there were still a few moist rales at the lung bases posteriorly and the liver was felt 2 cm below the costal margin. In the evening of December



Fig 97—In this figure are reproduced x-ray photographs of the chest of patient R N., New York Hospital History No 45479. Photograph A was taken on December 11, 1933, and shows diffuse mottling. This photograph was taken with a portable x-ray apparatus. Photograph B was taken on December 18, 1933, after the patient had improved. The lung markings are less dense in this photograph.

19th, the patient coughed up about 15 cc of bloody mucus and a small amount again during the morning of December 20th. Associated with this there was no rise in temperature, the ventricular rate rose slightly, however, the first evening but fell again at once. No change in pulmonary signs occurred. The use of digitalis was continued and the lungs became free of rales and the liver could no longer be palpated, he was discharged January 7, 1934, after sitting up for seven days. At this time the diffuse mottling which was present in the earlier x-ray photograph of the chest had disappeared (Fig 97, B). On this admission, then, the outstanding signs and symptoms were *frank hemoptysis, rapid ventricular rate, rise in temperature, leukocytosis, and*

*the presence of a few râles at the lung bases and dramatic improvement following digitalization*

The diagnosis on this admission was *Etiologic* Rheumatic fever (?) *Anatomical* Mitral stenosis and insufficiency, cardiac enlargement, right axis deviation. *Physiologic* Auricular fibrillation *hemoptysis associated with acute heart failure*

The third admission of this patient occurred on January 21 1934 and the discharge on January 29 1934. Following discharge from hospital digitalization was maintained and the patient slowly improved. On January 20th the day before the third admission he went out for the first time. This involved walking *up and down stairs*. When he reached home he was very short of breath and began to *spit blood*. He experienced *no pain*. During the next day and the day of admission he coughed up *4 cups of bright red blood* mixed with sputum. The blood was fresh it tasted salty and warm. In the afternoon of January 21st, when the temperature rose to 104° F and he became nauseated and vomited he was admitted to the hospital at 7 P. M.

On admission the temperature was 103.8° F (mouth). The ventricular cardiac rate was 128 per minute the radial 78. The systolic blood pressure was 112 mm of mercury the diastolic, 55. The respiratory rate was 30 per minute. He appeared acutely ill. There was cyanosis. The veins of the neck were *not distended*. There were signs of cardiac enlargement and of mitral stenosis and insufficiency, rapid auricular fibrillation was present. There were signs of a moderate degree of congestion at the lung bases posteriorly. A friction rub was *not heard*. Ascites was not present the liver was palpated 4 cm below the costal margin edema of the extremities was not present. The count of the white blood cells was 17,000. 54 per cent of these were adult and 33 per cent immature polymorphonuclear cells 8 per cent lymphocytes and 5 per cent monocytes. The count of the red blood cells was 3,800,000 and the estimation of the hemoglobin 13 Gm. The urine was negative. On being placed at rest in bed the temperature had fallen promptly to normal by the next morning (Fig 96 January 21st and following) and remained normal during the day rose slightly to 101° F the following morning (January 23rd) and then fell to normal and did not rise again. The ventricular rate fell promptly to normal and remained low. Digitalization was maintained. On January 2nd the count of the white cells was 9700 on January 23rd, 10,600 and then fell to 8000 on January 27th. The patient's general condition improved in a fashion parallel to these changes. Frank hemoptysis did not occur after admission to the hospital. Neither cough nor sputum containing blood was present after the morning of January 23rd. On January 25th a few râles only were present at the lung bases posteriorly and the liver was felt 3 cm. below the costal margin. x Ray photograph of the chest on January 22nd showed diffuse mottling but *no evidence of pulmonary infarction or pneumonia*. On January 28th the chest was free of râles. The liver was no longer palpable and on January 29th, the patient was transferred to Kingsbridge Veterans Hospital for convalescence with advice to continue the use of digitalis.

This episode, as was also the preceding one was characterized by pulmonary hemorrhage coming on after overexer



tion, and accompanied by rapid heart rate, fever, leukocytosis, signs of pulmonary congestion, and characterized finally by the rapid disappearance of these signs and symptoms when the patient was placed at rest in bed. In this instance again, hemoptysis occurred as a sign of acute heart failure.

The fourth admission of this patient to hospital occurred on June 10, 1934, at 7 24 P M, he died four hours later at 11 26 P M. He complained of dyspnea and of spitting up *frothy pink sputum* for one day.

**Interval History**—The patient was discharged to Kingsbridge Veterans' Hospital on January 29, 1934, for convalescence, and remained there until April 28, 1934. He remained in bed most of the time until May 20, 1934, when he increased his activities and began to go for walks. Digitalis was continued. On June 3, 1934, one week before admission, he developed cough and sputum after taking a short walk and felt very ill. He remained in bed two days and then went for another walk. Again he felt worse and because the cough was more pronounced he remained in bed. On June 8, 1934, swelling of the feet was observed. On the morning of June 10th, he suddenly began to sweat, and the heart rate which had until now remained slow increased to 102 per minute. He vomited four times during the day. On the day before admission to the hospital the sputum became tinged with blood and on the afternoon of admission it became *frothy and pink in color*.

The patient was admitted to hospital in a semicomatose condition, the respirations were gasping. The lips and nail beds were cyanotic. He spit up frothy pink sputum and drooled pink mucus from his mouth. The percussion note over the chest was resonant, and there were coarse moist bubbling râles heard all over the chest. They were audible at a distance from the patient without the application of a stethoscope. Rapid auricular fibrillation was present. The patient was obviously suffering from pulmonary edema. In spite of the withdrawal of 750 cc of blood by vein, the administration of digitalis per rectum, and the use of the oxygen tent, the patient died of pulmonary edema four hours after admission.

The outstanding symptom then on this admission was the profuse frothy pink sputum characteristic of pulmonary edema.

**Summary of Autopsy**\*—*Primary Anatomical Diagnosis*—Chronic endocarditis and calcification of mitral valve with mitral stenosis and insufficiency, hypertrophy and dilatation of heart, *congestion and edema of lungs*, bronchopneumonia, acute mediastinal lymphadenitis, pleural effusion, bilateral (200 cc), pericardial effusion (90 cc), chronic congestion of spleen.

*Accessory*—Multiple old infarcts of kidneys, perisplenitis, mild, fibrous scar of apex of left lung, atheroma of aorta.

\*The autopsy was performed by Dr. Charles T. Olcott.

The description of the heart and lungs only need be given in detail

*Heart*—The heart was normal in location except for the transverse enlargement which was most evident in the *right ventricle*. Its measurements were 13.5 cm in length, 12.5 cm in breadth 7 cm in thickness. Its weight was 690 Gm. The left auricle was enormously dilated and contained fluid blood. The right auricle was dilated but less so than the left and it contained post mortem clot. The mitral valve was of buttonhole shape its cusps almost completely calcified. The cusps were very irregular and folded over on themselves. The lumen was 11 by 7 mm in size. The tricuspid valve was moderately dilated and was 13 cm in circumference. The cusps were not thickened. Their cusps were within normal limit. The left ventricle was 1.8 cm in thickness the lumen was of approximately normal size while the right ventricle was 0.7 cm in thickness. The musculature of both was normal in color. On *microscopical examination* nothing unusual was found. Aschoff bodies were not seen in the sections examined.

*Lungs*—The right lung weighed 1100 Gm. the left 950 Gm. Both were soggy throughout more so in their posterior aspects, the right more than the left. No areas suggestive of *infarction* were found on external examination. The lungs on section showed no areas of consolidation or *infarction*. On *microscopical examination* of the lung marked congestion and edema and areas of early hypostatic pneumonia were found.

In this patient suffering from mitral stenosis, therefore, there were four episodes associated with splitting of blood, a first due to Type III pneumococcal pulmonary infection, the next two characterized by frank hemoptysis associated mechanically with acute heart failure, and finally the fourth and terminal one associated with pulmonary edema. That none of these episodes were due to pulmonary infarction was conclusively demonstrated at autopsy examination, since no scars of pulmonary infarction were found.

To summarize, the autopsy, therefore, in this patient who on four occasions had suffered from the symptom of blood in the sputum, the first occasion associated with pneumonia, the next two with acute heart failure, and the fourth with pulmonary edema, did not reveal evidence of old or recent pulmonary infarction.

The case of the second patient to which I wish to call attention is M. H., the Hospital of the Rockefeller Institute No. 4932 a white Jewish male.

I take this opportunity of thanking Dr. Alfred F. Cohn of the Hospital of the Rockefeller Institute New York, for his kind permission to report the case of this patient as well as of the one following.

aged twenty years, who was first admitted to Hospital of the Rockefeller Institute February 1, 1924, discharged May 29, 1924. He complained of shortness of breath since November 30, 1923, and pain in the heart since October 15, 1923.

**Family History**—One sister died at nineteen years of age of rheumatic heart disease.

**Past History**—The patient enjoyed excellent health until the onset of the present illness. Five years before this he was granted life insurance and his heart was said to be normal. History of rheumatic fever and its manifestations could not be elicited.

**Present Illness**—On December 15, 1923, the patient, while working as a shipping clerk, lifted a heavy case. He felt something "tear" beneath the upper part of his sternum, he coughed and brought up phlegm consisting for the most part of *bright red blood*. He experienced slight precordial pain. Thereafter cough persisted and each time was accompanied by expectoration of *bright red blood*, the amount of blood gradually increased. He continued at work for two weeks suffering from cough and expectorating bloody sputum, during this time he was slightly short of breath after lifting things or going up stairs. On October 30, 1923, the patient felt weak. At 3 A. M. on November 1st, he was awakened by a sensation of heaviness in the chest. He states that he "tried to cough the heaviness off," and then brought up lumps of dark blood followed by red blood, he was conscious of it welling up in his mouth. He experienced pain over his heart and palpitation. He brought up *in all more than a glass of blood*. He remained in bed and for four days afterward brought up blood in the sputum, the amount of blood decreasing and, finally, disappearing entirely. While he was up out of bed two weeks he suffered from palpitation and cough, although he did not limit his activities, he did not return to work.

On November 30, 1923, he was running for a car and suddenly felt short of breath. This symptom persisted. On December 3rd, he began to cough and then to *sput blood* and again became aware of palpitation and went to bed. He was admitted to Fordham Hospital on December 5th because of these symptoms. They persisted for a day or two after admission to the hospital. Digitalis was administered. After three weeks in the hospital he was discharged to a convalescent home where he engaged in all the activities, such as dancing and walking. The use of digitalis was discontinued. There was recurrence of dyspnea and of precordial pain and he sought admission to the Hospital of the Rockefeller Institute on February 1, 1924.

**Summary of Examination**.—The temperature was 101° F (rectal). The ventricular heart rate was 130 per minute, the radial 80. He was dyspneic, cyanosis was not observed. The rhythm of the heart was that of auricular fibrillation. There were signs of mitral stenosis and insufficiency. The heart was enlarged. With the exception of a few râles at the extreme bases on deep breathing, the lungs were normal on examination. The liver was not palpable. Edema was not present. In the x-ray photograph of the chest the heart had the configuration typical of mitral stenosis and was enlarged. The electrocardiogram showed auricular fibrillation, right axis deviation was present. On administration of digitalis the temperature fell, the lungs became clear and



heart failure recurred, shown by enlargement of liver, edema, cyanosis and dyspnea, he became worse rapidly and he died May 10, 1928. Permission for autopsy was granted. This examination confirmed the anatomical diagnosis of mitral stenosis. The examination of the lungs did not reveal *pulmonary infarcts*. The diagnosis made on gross and microscopical examination was chronic passive congestion and edema of the lungs.

This second patient also falls into that group of individuals suffering from mitral stenosis and auricular fibrillation who exhibit hemoptysis as the prominent symptom of acute heart failure. The autopsy report was cited to demonstrate that recurring pulmonary infarction did not account for the occurrence of hemoptyses.

I wish to recount briefly the history of a third patient still, who presented hemoptysis as a symptom of acute heart failure, and in whom there is evidence that the expectoration of blood was not due to pulmonary infarction.

F McG., Hospital of the Rockefeller Institute, No 6287, was a white male, twenty years of age, first admitted to the Hospital of the Rockefeller Institute January 19, 1925, complaining of shortness of breath and "fluttering" of his heart since Thanksgiving, 1924. There was no history of rheumatic infection and there was no knowledge of the presence of heart disease until the symptoms mentioned above occurred following overexertion. He exhibited, on admission, signs of mitral stenosis and insufficiency, aortic insufficiency, cardiac hypertrophy, and of mild cardiac failure. Dyspnea and cyanosis were present, rapid auricular fibrillation was present, the lungs were free of rales, the liver was not palpable, there was no peripheral edema. The symptoms were relieved by the use of digitalis and the patient was discharged May 10, 1925. The x-ray photograph on this admission showed an enlarged heart which was of the form characteristic of mitral stenosis. The patient was admitted to the hospital a second time from February 27 to March 24, 1927, because of a second attack of cardiac failure characterized by shortness of breath.

On February 3, 1928, he was admitted again to hospital for a third time. Three weeks before this he began *sputting blood*. The bloody sputum continued for ten days, and because of it he remained in bed. When he came to the hospital for follow-up examination on February 3, 1928, it was found that he was not taking sufficient digitalis to maintain the heart rate slow and he remained in the hospital that this might be regulated. There was cyanosis, the lungs were clear, the liver was not enlarged, there was no edema. During this admission it was decided to remove the tonsils which were much enlarged, this was done under gas-oxygen ether-chloroform anesthesia. The patient recovered rapidly from this operation and began sitting up two weeks

after the operation Three weeks later still on May 5 1928 while the patient was sitting in a wheel chair he died suddenly without any premonitory sign. Autopsy examination did not reveal a satisfactory explanation for the sudden death infarcts were not found in the lungs or in the brain Status lymphaticus was present Death probably was the result of ventricular fibrillation The autopsy examination confirmed the diagnosis of mitral stenosis, old endocarditis of the mitral and aortic valves the lungs on both gross and microscopical examination revealed chronic passive congestion and edema only There was no evidence either of old or recent pulmonary infarction

This case illustrates once again the occurrence of pulmonary hemorrhage as a sign of heart failure in a patient suffering from mitral stenosis

I have presented three cases all of which have these factors in common (1) The presence of mitral stenosis as the predominant valve lesion, (2) auricular fibrillation as the cardiac rhythm, (3) the *frequent occurrence of blood in the sputum or hemoptysis*, (4) autopsy examination in each instance showed the lungs free of recent or old pulmonary infarction

Blood in the sputum has long been recognized as a manifestation of derangement of the circulation Textbooks mention more or less casually the occurrence of hemoptysis in the presence of mitral stenosis, but its importance as a symptom and especially as a sign of acute heart failure has not been given sufficient emphasis In many instances in which this symptom is presented pulmonary infarction is diagnosed even in the absence of the usual signs and symptoms associated with this lesion It is the *symptom* of hemoptysis as evidence of disturbance of the mechanics of the circulation that I wish to emphasize.

The features which seem to characterize the occurrence of this symptom as a sign of heart failure in patients with mitral stenosis are these (1) It usually comes on after either acute overexertion or prolonged periods of overexertion (2) The sputum may be streaked with fresh blood at first and later resemble pure blood large amounts may be expectorated as much as 500 cc in twenty four hours I have *not observed* under these circumstances the frothy and pinkish sputum which is characteristic of pulmonary edema patients may feel the

blood squirting with each heart beat or be aware of it welling up in the throat, and may be conscious of its warm salty taste (3) The hemoptysis or expectoration of blood-streaked sputum may be accompanied by a sense of stretching of the heart or by precordial distress (4) It is usually accompanied by increase in heart rate, by rise in temperature, and by leukocytosis It may occasionally be ushered in by the occurrence of a chill There may be a rapid fall in heart rate and temperature as the hemoptysis subsides (5) I have observed this sign as a profuse hemoptysis in patients as a result of a sudden strain placed on the heart by an acute upper respiratory infection (6) In the three patients reported the rhythm of the heart was auricular fibrillation, it occurs also, however, in the presence of normal sinus rhythm (7) During the period of blood spitting there may be a few râles at the lung bases, they are not present usually in great numbers, however, and there is no diffuse scattering of them throughout the lung such as occurs in the presence of pulmonary edema (8) The x-ray photograph of the chest may either show no abnormality or may reveal diffuse mottling which will clear within a few days as the symptom abates (9) There is usually the absence of *signs of congestive heart failure* (edema, ascites, pleural effusion), and this symptom in most instances occurs in patients who *do not* suffer attacks of congestive heart failure

Blood in the sputum under the circumstances illustrated by the cases of the three patients which have been recorded is different from the clinical circumstances surrounding its presence in pulmonary infarction The essentially *typical* clinical features characterizing this last situation are the sudden onset of pain in the chest, collapse, followed by rise in temperature, presence of pleural friction rub, leukocytosis, and within twenty-four hours the expectoration of *clear currant jelly sputum* and appearance of dulness over the area, and perhaps of the physical signs of consolidation The fall in temperature is usually by lysis and several days later *jaundice* may appear The occurrence of frank hemoptysis following even mass pulmonary infarction, although it sometimes occurs, is not very





to it an increased amount of blood, which the hypertrophied right ventricle in turn propels into the pulmonary circulation. This increased amount as we have seen probably cannot in the same period of time pass the stenosed mitral opening. The total amount of blood in the pulmonary vessels having filled all the reserve space available, and pressure in them having become greater than the vessels can withstand, pulmonary hemorrhage occurs. The notion that the right ventricle does not fail is given weight by the absence in these instances of very marked enlargement of the liver, absence of ascites, absence of edema, and of undue venous engorgement. The physical mechanism, as well, by which pulmonary hemorrhage occurs in these instances is not clear. Whether loss of blood from the pulmonary circulation occurs by rupture of vessels or by general diapedesis cannot be stated. This has recently been discussed by Proft.<sup>2</sup> Nor are the controlling circumstances or factors known which give rise, under one set of conditions of acute heart failure, to the frank hemoptysis in which what appears to be pure blood is allowed to pass out, and in another to the state in which pulmonary edema occurs, characterized by the extravasation or passing out from the blood stream of the fluid portion of the blood with a few laked red blood cells. The first patient cited exhibited both phenomena, frank hemorrhage and finally, on occasion of his last admission, typical pulmonary edema.

The prognostic implications are different, of course, in each of these types of pulmonary hemorrhage in the presence of mitral stenosis. For obvious reasons, the most important one for differential diagnosis is pulmonary infarction. In the case of pulmonary infarction the question of embolic phenomena arising from thrombi in the right side of the heart due to the slowed circulation, or endocarditis, or emboli from the peripheral veins arises. In estimating the prognosis in a series of cases of paroxysmal pulmonary hemorrhages, Oppenheimer and Schwartz state that two died within three years of the onset of these episodes. The duration of life after the onset of pulmonary hemorrhages in the patients which I have dis-

cussed is six months, four years, and three months, respectively. It is recalled that auricular fibrillation was present also in these patients. A statistical analysis to arrive at data for making a prognosis in the case of this symptom has not been made. In the case of the patients to which attention has been directed, it was an occurrence as we have seen toward the end of their life span. It may turn out, as De Graff<sup>3</sup> has shown to be the situation with regard to auricular fibrillation, that it is not an unfavorable prognostic sign in itself, but that it occurs after heart disease has existed for a long time, therefore, toward the end of the life span expected of that patient. The individuals who suffer from this symptom are not those in whom attacks of congestive heart failure, exhibited by edema, ascites, swelling of the liver, pleural effusion, have been outstanding features. Since the symptom appears more frequently after overexertion therapy directed toward this line may be of benefit in prevention. The three cases were selected for presentation because in them were autopsy examinations by which the incidence of pulmonary infarction could be eliminated.

Finally, if one wishes to think in terms of heart failure of the right or of the left side, it does not seem possible, to assign the origin of this symptom to the failure of either the one or of the other heart chambers. The left ventricle is limited in its output to the amount of blood that can arrive there through the narrowed mitral opening, the right ventricle in turn is limited in the amount that it can supply the left ventricle, in the situation now being discussed not by the amount that is available, which appears to be sufficient, and probably not by failure in contraction but by the amount it can pass on to the left ventricle through the stenosed opening in unit time. Even at a tremendous pressure, and at a very rapid velocity of blood flow, the total quantity of blood that can pass the stenosed opening in unit time is limited. And it appears in the three cases which have been presented, that the right ventricle performs its function without failing (in the usual meaning of this word with respect to right and left side failure) propelling the blood forward into the pulmonary circula

tion from which it cannot pass rapidly enough, in short, it performs its function perhaps all too well

**Note**—After the material for this clinic had been written and was ready for the press, I came upon the recent paper of McGinn and White (McGinn, S, and White, P D Amer Heart Jour, 9 697, 1934, Acute Pulmonary Congestion and Cardiac Asthma in Patients with Mitral Stenosis) in which they discuss the occurrence and mechanism of acute pulmonary congestion in the presence of mitral stenosis

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